



# BULLETIN

OF THE NEW YORK  
ACADEMY OF MEDICINE



*Original Articles*  
by

ALFRED N. RICHARDS

SELIG HECHT

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EDITORIAL  
PROCEEDINGS OF THE ACADEMY  
LIBRARY NOTES



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ACADEMY OF MEDICINE

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IN THEIR CONTRIBUTIONS

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# BULLETIN OF THE NEW YORK ACADEMY OF MEDICINE



JANUARY 1938

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## *EDITORIAL ANNOUNCEMENT*

THE Members and Fellows of the Academy, acting through their Council and Trustees, decided some time since on changing to some extent the nature of the BULLETIN. To this end a Board of Editors was appointed. For several years every function which the BULLETIN can serve has been carefully canvassed. As the result of many discussions and much planning, the BULLETIN appears in the first number of this new volume in a new dress. The new format is intended to symbolize the change, or the hope of change, which the BULLETIN is to undergo.

There is every reason to believe that the BULLETIN can be made to serve as the medium for reflecting the intellectual life and the activities of the Academy. Now, when the activities of the Academy have multiplied and its life has become richer, the need for developing its opportunities for publication have become apparent. Beside the Stated Meetings and the Section Meetings which constitute the backbone of its being, the Academy has affiliated with itself a number of cooperating scientific societies: the New York Roentgen Society, the Harvey Society, the Society for Experimental Biology and Medicine, and the New York Pathological Society. It provides, furthermore, series of lectures and discussions in many directions. The Annual Graduate Fortnight has become the occasion for presenting full reviews of subjects of active contemporary concern. It has come to engage the attention of large numbers of physicians in New York and elsewhere in the country. The

Academy houses the second largest collection of books of interest to medicine in the country, adding constantly to it whatever contributes to variety and value in medical learning. These large and varied activities give, and have given occasion for continuous meetings of physicians-practitioners and investigators—who in their reports and discussions provide a source whence flows a rich stream of learning and practical experience. The writings which come into being under these circumstances constitute the proper material for publication in the BULLETIN. Besides, accounts of the formal activities of the Academy will be suitably presented.

The Board of Editors will welcome especially reports of original researches undertaken by Members and Fellows of the Academy and by others wishing to use the good offices of the BULLETIN.

By following this plan, the usefulness of the BULLETIN will be much increased. From time to time editorial comments will appear, proposing, criticizing, appraising issues predominantly of scholarly interest, whether in the field of practice, administration or research. It is the intention in short to make of the BULLETIN a forum for discussion, on a high intellectual level, of matters having importance in the scientific and practical aspects of the life of medicine.

The Board of Editors is deeply indebted to Mr. David Silve for the imaginative quality he has displayed, for his understanding of the problems at issue, and the care with which he has planned this format, and to Mr. Charles C. Morchand, its publisher and printer, for his interest, his cooperative spirit and his unremitting unselfishness in bringing the new BULLETIN into existence. No detail has been too trivial to escape notice—the design of the cover, the several types of pages each appropriate to their subject matter, the typography, the selection of the paper on which can be reproduced all the usual forms of illustration, the form for references to scientific contributions and accessions to the library—all have been given due study. Especial attention is directed to the escutcheon designed by Dr. Dickinson, incorporated in the decorative border of the cover and printed in a different form on the opening page. The opportunity to utilize this forceful design in the scheme has contributed greatly to its success.

In this new dress the Board of Editors commends the BULLETIN afresh to the Members and Fellows of the Academy. It reminds them that on their active cooperation, the future of the BULLETIN must depend.

## PHYSIOLOGY OF THE KIDNEY

*The Wesley M Carpenter Lecture\**

ALFRED N RICHARDS

Professor of Pharmacology University of Pennsylvania

THE KIDNEY is chief pathway of exit from the body of water and of non-volatile diffusible constituents of the blood. Its function, broadly considered, is the maintenance of that constancy of composition of the internal fluid environment of the cells of the body which is essential not only for health but for survival. It shares this function with the respiratory system, the skin, the gastro-intestinal tract. It accomplishes its function by the elimination of urine, at widely varying rates and of widely varying composition. Some of the diffusible constituents of plasma appear in the urine in concentrations far higher than those which obtain in the blood, some appear in urine in scarcely detectable traces. It seems as though the kidney can excrete urine of almost any composition which the internal environment of the body requires (Adolph)

The remarkable constancy of the composition of blood plasma, maintained against the assaults of periodic intake of varied amounts of fluid, salts and food, of changing external conditions, of widely differing metabolic activities, constitutes proof in itself of the flexible adaptability of the kidney, not only to the ever present demands of the body for the excretion of useless or deleterious substances, but also of its adaptability to the constant need of the body for protection against loss of vitally important substances. The conserving capacities of the kidney, responsible for the retention of water, of inorganic bases essential for the preservation of the electrolyte balance of the blood and for the retention of diffusible food stuffs are quite as necessary for preservation of the constant state as is its capacity to excrete metabolic waste, unneeded salts and water, foreign substances occasionally introduced.

The capacity of the kidney to deal individually with each of a multiplicity of substances with discriminating effectiveness provides

\* Delivered November 1 1937 in the Tenth Annual Graduate Fortnight

intricate problems both in the integrative physiology of the body as a whole and in cell or organ physiology which are of fundamental importance. The literature contains voluminous accounts of experimental researches, the purposes of which have been to describe the range of activities of the kidney in terms of its response to changes in its mass, to changes in its blood supply or innervation and particularly to changes in the composition of the blood from which its product is elaborated. A mass of important information has resulted, useful to physiology and to medicine, which shows, for example, the magnitude of the factor of safety in the renal structures (normal renal function can continue after half or more than half of the normal structure is removed), the changes in function which result from changes in its circulation (the vascularity of the kidney is so great that as much as one-fourth of the total blood in the body may traverse the renal vessels every minute), the fact that apparently normal renal function is not dependent upon an extrinsic nerve supply. It reveals the remarkable rapidity with which many foreign substances are excreted and it has shown the quality and quantity of the responses which the kidney makes to excess or deprivation of water, salts, acid, alkali, urea, etc.

Such studies define the usefulness of the kidney as the excretory servant of the body. Out of them have come tests of kidney function, methods of recognizing disorder of the kidney and evaluating its extent and probable outcome. They yield little information however which identifies or defines the individual processes by which urine is formed and elaborated within the kidney. They have given us hypotheses only with which to relate excretory or conservatory processes with the different parts of the renal apparatus. The physiologist and the physician hope ultimately to know what processes are operative in the different parts of the renal unit, the nephron, what controlling circumstances govern their activities, how they are coordinated, not only within a single unit or among the myriads of units which constitute the kidney but how the mass activity of the whole organ is coordinated in such a way as to serve the body with such remarkable efficiency.

My working interests for many years past have expressed themselves in attempts to design experiments which might clarify my understanding of the nature and site of processes of urine formation within the kidney. Much of what I shall now have to say will represent the results of such attempts.

It seems almost obligatory to begin this discussion with allusions to the work of great predecessors in the past out of which present knowledge has developed

Bellini is said to have been the first to publish a description of the renal tubules in 1662. In 1666 Malpighi described the globular structures in the cortex which at once became known as the Malpighian bodies. He showed that they were connected with the arteries and guessed, but could not demonstrate, that they were connected with the tubules. Nearly two centuries elapsed before Bowman, a 26-year-old demonstrator of anatomy in London, proved by beautiful dissections that the Malpighian body is the expanded end—the beginning—of the renal tubule, that the intracapsular space is continuous with the lumen of the tubule. Impressed by the resemblance of the tubules to the acini of digestive glands, he conceived that the cells which compose their walls secrete the waste products of metabolism from blood into their lumina, the glomerular capillaries seemed to him peculiarly suited to permit the escape of water from the blood. From these two impressions he constructed the hypothesis that the urinous constituents of blood are secreted by the tubule cells and washed out of the lumen by a saline stream flowing down from the glomerulus.

Bowman's discovery was at once confirmed by another youngster of his own age and of comparable genius, Carl Ludwig. He examined the structures with the eyes of a physiologist whose ambition it was to interpret vital phenomena in terms of physics and chemistry. He saw the hydrodynamic possibilities of the arrangement of glomerular capillaries and boldly stated that this structure must be a filter, that the beginnings of urine formation consist in the separation of a cell-free, protein-free filtrate from the blood as it passes through the glomerular capillaries, in volume sufficient to contain all of the dissolved components of urine, that this filtrate in its passage down the tubule is concentrated by reabsorption from the tubule and issues into the pelvis of the kidney reduced in volume, increased in concentration, fully elaborated urine.

The significance of the work of these two young men can scarcely be overestimated. In the space of two years (1842-'44) physiology was supplied with a correct structural representation of the unit of kidney function and with two hypothetical conceptions of processes operative within it. A great part of subsequent experimental study has been influenced by these concepts and the results expressed in their terms.



During the following years experiments instigated by Ludwig, which showed the relations between changes in rate of urine output on the one hand and changes in arterial blood pressure or in ureteral pressure on the other, yielded results which were in harmony with his filtration-reabsorption theory. These, together with the influence of Ludwig, resulted in widespread acceptance of Ludwig's ideas. But in the years 1874-1883 work by Heidenhain of Breslau upset this view. He found that the diffusible dye, indigo carmine, injected intravenously into rabbits, is rapidly excreted in the urine in high concentration but is not detectable in the glomerular capsules seen in sections of the kidney, excised while excreting it. Hence he concluded that indigo carmine is not excreted through the glomerulus. It is a diffusible substance, therefore the glomerulus is not a filter but a secreting structure with the capacity of selecting what shall pass through it.

He reduced the blood pressure in rabbits by section of the spinal cord to a level which abolished urine elimination. Then, having injected indigo carmine, he excised the kidney, found massive accumulations of dye in the lumina of tubules, concluded that it could have found access to them only through the cells of the tubules, hence these are secreting cells.

He raised glomerular capillary blood pressure, not as Ludwig had done, by increasing arterial blood pressure, which also increases rate of blood flow, but by partially obstructing the renal vein, which decreases blood flow. He found that rate of urine flow always diminished. From this he argued that rate of blood flow through the glomerular capillaries rather than the blood pressure within them is the prime essential in the production of glomerular urine. It acts, he thought, by altering the state of nutrition of the epithelium which covers those capillaries.

He calculated the volume of filtrate from blood plasma which would be required to contain the amount of urea which a man excretes in a day. The figure arrived at was 70 litres. Of this, according to the filtration theory, some 68 litres must be reabsorbed if the day's output of urine were 2 litres. He did not believe that a volume of blood sufficient to yield 70 litres of filtrate flows through the kidneys in a day. He regarded such an uneconomical process as his figures indicated as incredible.

These facts and arguments and the skill with which they were presented caused physiologists throughout the world to recant their

faith in Ludwig, and for the next thirty years the physiology of the kidney was principally taught in terms of the Bowman-Heidenhain secretory theory

The literature of that period is a literature of debate. Neither the concept of filtration-reabsorption nor that of secretion could satisfactorily answer the objections of the one against the other. Experiments which compelled belief were lacking.

Between 1896 and 1917 work was published which had the effect of slowly reinstating the filtration doctrine in the respect of physiology. Of outstanding importance was Starling's classical demonstration of the osmotic pressure of plasma proteins, previously thought, because of the great size of their molecules, to be osmotically inert. He showed that their osmotic pressure amounts to some 30 mm Hg, i.e., when plasma is separated from isotonic saline by a membrane impermeable to protein but permeable to water and salt, fluid is drawn in to the plasma with an initial force of 30 mm, or if the attempt is made to filter plasma through a membrane impermeable to its proteins, a pressure greater than 30 mm Hg must be applied before any protein-free fluid can separate.

Starling then found that in diuretic dogs, urine formation ceases when arterial blood pressure is reduced to about 40 mm, that when the ureter is obstructed, urine continues to be formed until the ureteral pressure has risen to a level about 40 mm of mercury below that of the arterial pressure. The coincidence of these two values, and the fact that they approximated so closely to his values of the colloid osmotic pressure of plasma led him to think that the plasma proteins interposed an obstacle to the formation of urine of the same sort as that which they interpose to filtration through a membrane, in a word, that a process of filtration is concerned in urine formation.

Experiments by Bambridge showed that whereas normal frog's urine is strongly hypotonic to plasma, when the tubules (but not the glomeruli) are poisoned with bichloride of mercury, the urine becomes isotonic. His inference was that the glomerular urine is a filtrate which is rendered hypotonic by reabsorptive processes in the tubule.

Another important influence was the publication in 1917 of a monograph on the Secretion of Urine by Cushny. He made an exceedingly thorough critical analysis of existing experimental evidence which, while it exposed the deficiencies of the evidence for both theories, revealed greater weaknesses in the basis of the secretion doctrine than in that

of filtration-reabsorption. From this analysis Cushny developed a modification of Ludwig's ideas which he termed the Modern Theory and which found widespread acceptance.

Thus, some twenty years ago, physiology found itself in possession of hypothetical concepts of renal function, of an enormous mass of experimentally acquired information bearing upon these, but still unable, with decisive certainty, to answer some of the simplest, most direct questions which had been confronting her from the moment when the true relationship between glomerulus and tubule was discovered.

Does the glomerulus play a passive or an active role in urine formation? What is the extent of its participation? Do the tubule cells secrete material from blood to lumen of tubule or do they secrete constituents of the glomerular product back into the blood from the lumen of the tubule, or do they do both? Is there a division of function in the different, structurally unlike parts of the tubule?

These are precisely the questions which troubled Bowman, Ludwig, Heidenham, Starling and Cushny—they are still of great concern to us, though distinct progress has, I think, been made toward their solution in the past twenty years, it is of this progress which I now wish to speak.

First concerning the nature of glomerular function.

If we knew with certainty the differences between the composition of the plasma of the blood flowing through the glomerular capillaries and that of the fluid which separates from it at that point, we should know at once whether the glomerular membrane behaves like a filter or whether it exhibits capacities of retarding or of accelerating the passage of individual components of the plasma through it. If in addition we knew the volume of this separated fluid which is delivered into the tubules we should be able at once to define the task of the tubules, at least in general terms.

In the autumn of 1921 workers in my laboratory found themselves in possession of two techniques which had not previously been used in the study of the kidney, both adaptations of methods used in other connections by other workers. One was a method of microscopic observation of the frog's kidney during life, similar in design and purpose to that which Krogh had utilized in his studies of capillaries, indeed to that which, long ago, Malpighi had used in his discovery of the capillary connections between arteries and veins. The other was a micro-dissection method, a somewhat crude though effective modification of that which I

had seen Robert Chambers using in his manipulations of single cells, by which it was possible to insert sharply pointed tubes into the space within Bowman's capsule and to abstract the fluid which issues from the blood of the glomerular capillaries. The amounts of fluid thus obtainable were small—usually less than 0.001 cc—but it was easily possible to submit them to simple qualitative chemical tests, conducted in capillary tubes. The results showed that the glomerular fluid is free from protein but contains chloride and glucose, both of these being absent from bladder urine. It is alkaline, contains urea, and indeed every diffusible constituent of plasma for which we were able to make a test.

With time and patience it became possible to adapt to these small quantities of fluid a number of quantitative methods for the determination of individual constituents with highly satisfactory accuracy, and as a result we now have a fair number of quantitative comparisons of the concentrations of individual plasma solutes in glomerular urine and in plasma of frogs and *Necturi*, simultaneously collected from the same animal.

The results show that glomerular urine collected both from frogs and *Necturi* has the same composition as a plasma ultrafiltrate with respect to total concentration of solutes (vapor pressure), total electrolytes (electrical conductivity), pH, chlorides, inorganic phosphates, glucose, urea, uric acid, creatinine, phenol red, indigo carmine and inulin. The last five substances were injected subcutaneously or intravenously before beginning the collection of glomerular urine.

These results seem to me to leave little room for doubt that, in amphibia, the glomerular urine actually has the composition of a protein-free filtrate from plasma, precisely as Ludwig had imagined ninety-three years ago. They show that, so far as the frog is concerned, Heidenhain was wrong in denying that indigo carmine escapes from the blood through the glomerular membrane. They give no evidence that the glomerulus possesses any capacity whatever of selecting what substances shall or shall not pass through it if only they are diffusible.

I call particular attention to the fact that the results with inulin are wholly similar to the rest. This is a polysaccharide of high molecular weight (5100), consisting of some 32 levulose groups probably put together in the form of a chain. Its diffusibility through membranes is much slower than is that of urea, glucose or NaCl in free diffusion experiments (i.e., conducted with no membrane) its mobility corre-

sponds to that of a spherical molecule of 15,000 molecular weight (Bunim and Smith) The fact that this large and slowly moving molecule passes through the glomerular membrane at the same rate as does that of urea, which is only  $1/85$  as heavy and far more mobile, yields two conclusions one, that the passages or pores through the membrane are far larger than is necessary for the escape of the normal, diffusible constituents of plasma The membrane is a relatively wide-meshed sieve Another, that diffusion plays no significant part in determining the composition of glomerular urine as I am sure it does in determining that of fluid separated from blood in the systemic capillaries

Another important piece of cognate information was obtained by Hayman He succeeded in measuring the blood pressure in the capillaries of a single glomerulus by an application of the principle of the Riva-Rocci sphygmomanometer He closed the neck of the tubule, through a capillary pipette in the capsular space raised the pressure within Bowman's capsule to a height at which corpuscles were seen to be flowing through only two or three of the capillary loops instead of all the six which they usually contain and found that on the average, the glomerular capillary mean pressure is 54 per cent of the aortic pressure The average aortic pressure was found to be 37 cm of water, so glomerular capillary pressure is about 20 cm The colloid osmotic pressure of frog's plasma, which is the pressure which must be exceeded before a protein-free fluid can be separated by filtration through the glomerular membrane, is less than 10 cm These figures demonstrate that the blood pressure in the glomerular capillaries is ample to produce a filtrate

These analyses, the figures for capillary pressure, together with the results of numerous experiments on the surviving frog's kidney which show correlation between urine rate and height of aortic pressure lead me to think that for these amphibia we have no choice but to decide that the glomerular urine is an ultrafiltrate and that the process by which it is formed is the purely physical process of filtration

Direct measurements of the volume of filtrate formed in the sum total of the glomeruli of a frog's kidney have not been made A single glomerulus, however, will often yield 1 cu mm per hour, occasionally as much as 4 or more cu mm per hour If these figures are multiplied by the average number of glomeruli which the two kidneys of frogs such as we have used contain (4,000), we get an hourly volume of

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glomerular filtrate of from 4 to 16 cc. The rate of urine excretion in normal frogs immersed in water is much less than this of frogs subjected to the procedures necessary for collection of glomerular urine very much less. Indirect determinations indicate that in frogs the volume of the glomerular filtrate may be as much as 15 or 20 times that of the urine which is elaborated from it. I think we need not hesitate to conclude that excreted urine in amphibia is less in volume than the filtrate from which it is elaborated.

I wish now to question whether there is evidence upon which to base a conviction that the conclusion drawn from the amphibian experiments that the glomerulus is a filter can safely be carried over to the mammalian or human kidney. But before doing so it will be of advantage to discuss one aspect of the physiology of the renal tubule, viz secretion.

You will recall that Bowman regarded the tubule cells as secretory because of their appearance. Heidenhain, because of their capacity to accumulate indigo carmine within their lumina under circumstances which he believed abolished glomerular function entirely. Other evidence could be outlined, none however as convincing as that provided by the work of E. K. Marshall and his colleagues in Baltimore.

Marshall was aware of the fact that there are fishes whose kidneys consist only of tubules, no true glomeruli being present. *Lophius piscatorius*, the goose fish, and *Opsanus tau*, the toad fish, are those which he studied. These kidneys secrete urine at slow rates which contains urea, creatine and other nitrogenous substances, magnesium, sulphates, highly variable amounts of chloride and phosphate. When creatinine or phenol red are injected these appear in the urine in high concentration. Glucose, injected even in large amounts, is not excreted nor do the fishes become glycosuric when injected with phlorhizin. The chief blood supply of these kidneys is venous and the pressure of urine in the obstructed ureter may rise higher than the blood pressure. In these animals there can be no doubt that the tubule cells are secretory structures.

In work on dogs, Marshall showed with comparable certainty that the rate of excretion of small doses of phenol red, subcutaneously injected, is far too great to be explained by glomerular filtration, that the tubules must play a major part in the transfer of this substance from blood to urine.

For example, in one dog, the amount of phenol red excreted in one

minute was equivalent to that contained in 148 cc of plasma. Only one-fourth of the phenol red in the plasma was filtrable, three-fourths being combined with the plasma proteins. Hence, to account for the observed rate of phenol red excretion by filtration alone, a filtrate in volume equivalent to *all* of the plasma water from nearly 1200 cc of the blood would be required. It is clearly impossible that all of the water can be filtered out of the plasma in its passage through the kidney, equally impossible to conceive that enough blood flows through the kidneys per minute to yield 1200 cc of filtrate. Hence the inescapable conclusion that the tubules participate in the excretion of this dye. As a result of these experiments it is now possible to say with complete conviction that when small doses of phenol red are given to dogs, from 90 to 95 per cent of the dye is excreted by the tubules, only 5 to 10 per cent through the glomeruli.

Professor Homer Smith has shown that a similar statement can be made concerning man, and experiments made in my laboratory indicate that this general conclusion is applicable also to the excretion of indigo carmine in rabbits and of the organic iodine compound known as Hippuran in dogs.

Now to revert to the question whether the evidence permits us to believe that the glomerular process in mammals and in man is one of filtration.

(1) Microscopic study of the glomerulus in the human kidney shows no evidence of the existence of other structures or of more complex cell structures than are to be found in the frog's glomerulus. The epithelium which invests the capillary loops of the glomerulus in man is distinctly less conspicuous than in amphibia. There is no histological evidence of the development of structures which conceivably might serve a more selective process.

(2) The older experiments of Ludwig showed that the mammalian kidney resembles a filter in its response to changes in arterial blood pressure, within limits, urine rate increases and decreases with increase or decrease of blood pressure in the renal artery. The inference that this fact pointed to filtration as a factor in urine formation was contested by Heidenham in the belief that the simultaneous alterations in blood flow were the variations which caused the urinary changes. This contention has been answered by experiments with rabbits in which artificial arrangements were established which permitted blood pressure

in the renal circulation to be altered independently of changes in blood flow. They showed that when the volume of blood flowing through the renal vessels was kept constant, the rise of pressure in the renal circulation which was produced by nerve stimulation, by the effect of a small amount of adrenalin or by moderate obstruction of venous outflow from the kidney was paralleled in striking fashion by concurrent changes in rate of urine output.

(3) Heidenhain's claim that the diffusible dye, indigo carmine, is not excreted by rabbits through the glomerulus, a claim recently upheld by Professor Bensley of Chicago, is, I believe, based on inadequate experiment. This dye, like phenol red, is to a large extent bound by the plasma proteins, hence a large fraction in the plasma is not filtrable. The curve of its concentration in plasma after an intravenous injection falls very rapidly, so that if one allows a half-hour to elapse between intravenous injection of even a large dose and excision of the kidney for histological examination the concentration of filtrable dye in the plasma may be so low that a filtrate in the capsules at the time of excision gives no color to them which is distinguishable in fixed sections. Furthermore, when experiments are designed in which these two sources of possible error are avoided, clear evidence is obtained that indigo carmine is excretable through the glomerulus in rabbits, its membrane having no selective power to retard its passage.

(4) Finally, study of the renal excretion of the polysaccharide inulin gives evidence which is more than suggestive that mammalian glomerular process is solely one of filtration.

In frogs it was shown that with respect to every one of a considerable number of substances tested the glomerular urine gives evidence of being a filtrate. Among these was the polysaccharide inulin which despite its high molecular weight (5100) and low diffusibility passes through the membrane as rapidly as does the water in which it is dissolved or as do the far smaller molecules of urea, glucose, etc. This necessitates the inference, already stated, that the glomerular fluid is forced out of the blood through openings large enough to interpose no hindrance to these large molecules. In addition it appears that the majority at least may be even larger than this for when crystalline egg albumin (molecular weight 40,000-44,000) is introduced into the renal circulation of frogs it appears in large quantities in the urine, and is detectable in the glomerular fluid in concentration which seems to be



somewhat less than that of the perfusion fluid. But when crystallized horse serum albumin (molecular weight 68,000) is similarly tested none appears in urine or in the glomerular fluid. These statements give a rough definition of the frog's glomerular membrane, regarded as a sieve. If analogous results can be obtained in mammals, we can be permitted to think of the mammalian membrane in the same terms.

Now when inulin with a molecular weight of 5100 and a diffusion coefficient equal to that of a spherical molecule three times as large, is injected intravenously into dogs, it is excreted with great rapidity and often in very high concentration. For example, in one experiment 70 per cent of an injected dose of 14.5 gm. was excreted in 45 minutes. When egg albumin (molecular weight 40,000) is injected into dogs along with an equal amount of inulin its excretion is slower than that of inulin, though eventually quite as complete. When horse serum albumin (molecular weight 68,000) is injected, scarcely detectable traces of this protein appear in the urine. From this it would appear that the mesh of the glomerular membrane in dogs is approximately the same as in frogs, provided, however, that we can be sure that none of these large molecules are secreted into the urine through the tubule. So far as the egg albumin is concerned, I know of no evidence that it is excreted through the agency of tubule cells, much, chiefly histological that it escapes through the glomerulus. Concerning inulin, there is a good deal of evidence that none is excreted by tubules, all by the glomeruli. In part, it is this:

(1) The aglomerular kidney of the toad fish is wholly unable to excrete it, even when injected intravenously in large doses.

(2) The frog's kidney is unable to excrete it when it is presented to the tubules only via the renal portal vein.

(3) In dogs and rabbits, whose blood pressure is lowered to a level at which glomerular filtration is impossible, i.e., to that equivalent to the colloid osmotic pressure of plasma, injected inulin does not find its way into the lumina of tubules, whereas simultaneously injected phenol red, or indigo carmine, or Hippuran does.

(4) The rate of excretion of inulin in relation to its concentration in plasma, i.e., its plasma clearance, in dogs and rabbits, is identical with that of creatinine. In animals made diabetic with phlorhizin its clearance is identical with that of glucose (Shannon). It seems incredible that a tubular process of secretion, which we must regard as selective,

should deal in identical fashion with three substances so widely different physically and chemically as inulin, creatinine and glucose, whereas the physical process of filtration must inevitably deal with them alike, provided only that the filter is permeable to all alike, as, in frogs, we have found that it is

For these several reasons then we may regard the mammalian and the human glomeruli as filters with nearly as sure conviction as that which we hold concerning the amphibian glomerulus

If the facts and conclusions which have been outlined, particularly concerning the excretion of inulin, are true, viz that its sole pathway of renal excretion is the glomerulus and its concentration in the glomerular urine is the same as that in the water of the blood plasma, then we have acquired a trustworthy method for measuring the rate at which the glomerular filtrate is formed and delivered into the proximal ends of the uriniferous tubules

The amount of inulin excreted in the urine in a minute divided by the amount contained in 1 cc of plasma (i.e., plasma filtrate) gives the volume of filtrate in cc per minute

Many such determinations have now been made, most of them in the laboratory of Professor Homer Smith at the New York University Medical College and they show that for adult man under basal conditions 120 cc per minute is the average rate at which glomerular urine is formed. This value is obtained whether urine is being excreted at the rate of 0.5 cc per minute as a result of water deprivation or 15 cc per minute because of excessive water intake, or at intermediate rates

We have arrived at last at a conclusion substantiated by a large volume of evidence and at variance with none of which I am aware, which seems to me to be of paramount importance in any consideration of kidney function viz the beginning of urine formation consists in the separation from blood of a torrent of undifferentiated filtrate by a blind physical force. Its volume is so great as to contain all of the normal constituents of plasma which must be excreted, with the probable exception, for man, of a fraction of the creatinine, it contains also relatively vast quantities of glucose, amino acids and salts which must not be excreted. In the cells of the tubules reside the capacities of restoring to the blood by finely adjusted selective processes of reabsorption those substances which the body must keep. In tubule cells also reside secretory capacities which are responsible for the excretion of

a fraction of injected or ingested creatinine (in man) and of most or much of some foreign substances, of which phenol red may be taken as typical. In the present state of our knowledge we are not required to believe that any of the urea, uric acid, anions or fixed bases are normally secreted into the urine by the tubule cells.

When we find ourselves forced to believe that for the formation of 1 cc of urine per minute more than 100 cc of fluid are separated from the blood, that in this separated fluid are contained in 24 hours nearly half a pound of glucose, of bicarbonate, and two pounds of salt, little, if any, of which escape into the urine, we are compelled to realize that reabsorption is the chief task which the tubule is normally required to perform.

Direct evidence of the existence of reabsorptive processes and of the localizations of some has been obtained in the study of the amphibian kidney.

The same methods which were successful in providing fluid from glomerular capsules in frogs and *Necturi* have also yielded supplies of fluid drawn from different levels of the tubules of these animals. The experiments were far more difficult, however, because of the tortuosity of the tubules and the fact that each is intertwined with its neighbors, because of the narrowness of the lumen, and the necessity of avoiding collection of fluid which had flowed past the point of the collecting pipette, because of the necessity also of accurate identification of the site of puncture with reference to the nephron as a whole. A single nephron was identified by injecting dye into Bowman's capsule and watching its passage through the tubule. The deposition of a globule of mercury or oil in the lumen at a point immediately distal to the point of the pipette prevented reflux, a camera lucida scale drawing of the punctured tubule was made by filling its entire lumen with india ink, fixing the kidney and clearing the part containing it. The puncture hole was easily visible in the cleared preparation and measurements of the distances to the ends of the segment of tubule in which it occurred were accurately made. Obviously the analytical methods developed in connection with the glomerular problem were equally applicable to fluid from the tubule.

Before stating results it should be emphasized again that the urine of amphibians is always, normally, more dilute than the glomerular filtrate. This is largely due to absence of chloride and bicarbonate from

the urine. It doesn't necessarily mean, however, that the processes of urine formation in amphibia are unlike those in mammals. Frog's urine always contains urea in higher concentration than blood—under conditions of dehydration as much as 70 times that of blood. The balance between processes of reabsorption and those of concentration is different in two orders, there is no reason for thinking that the nature of the processes is different.

One group of results shows that the glomerular filtrate passes through the entire length of proximal convoluted tubule with little change, either in the total concentration of dissolved substances or in the concentration of chloride. It is only during passage through the lumen of the distal convoluted tubule that the total concentration and the concentration of chloride diminish. From these analyses it is possible to assert that the selective, active reabsorption of NaCl in amphibia is a definite function of the distal and not of the proximal convoluted tubule.

In striking contrast with the behavior of chloride is that of glucose. As soon as the glomerular filtrate has progressed an appreciable distance along the proximal tubule, its glucose content is significantly diminished. When half way through, the reabsorption appears to be complete or nearly so. Special experiments in which glucose solutions were perfused through the distal half of the proximal tubule and also through all of the distal tubule showed that the capacity of reabsorbing glucose is possessed by all of the cells of the proximal tubule but not by any of the cells of the distal tubule (Drs. Walker and Hudson).

The reaction of the fluid in the tubule remains essentially the same as that of blood plasma during its progress through the entire proximal tubule (Drs. Montgomery and Pierce). At a certain point in the distal tubule it begins to become acid. By injecting indicator solutions (phenol red) into the distal tubule, Dr. Montgomery found that the cells which are responsible for the acidification of urine are localized in a region corresponding roughly to the middle third of the distal tubule. There are the best of reasons for believing that reabsorption of base from the tubular fluid is responsible for its acidification.

Visual evidence was long ago obtained of reabsorption both of base and of water. The lumen of a single tubule was distended with a dilute solution of phenol red by intracapsular injection. The tubule was blocked by pressure with a glass rod so that no more fluid could enter the tubule, that within it remained stationary. The colored streak which revealed the

lumen gradually changed from a broad, lightly colored band to a narrow thread of concentrated color. Fluid was leaving the lumen, the dye was retained within it. The color remained red until the blocking rod was lifted. Then the column of fluid moved on down the tubule and its color changed abruptly to the yellow tint, which represents acidity, at the level in the distal tubule at which, we must believe, base is reabsorbed.

These reabsorptive processes are abolished when the tubule cells are poisoned as by HCN or  $\text{HgCl}_2$ . They are not to be explained by diffusion or, so far as I am aware, by any other familiar physical process. They continue to operate when the fluids within and without the tubule are of identical composition, i.e., when no initial diffusion gradients exist.

The time which was allotted to me is past. Evidence has been outlined which seems not only to justify but to necessitate belief that the first function of the kidney is to separate a filtrate from blood in volume so enormous as to contain all of the waste products of metabolism and the unneeded salts and water. Necessary as this function is, were it uncorrected, death from dehydration and loss of bases would inevitably and promptly ensue.

Corrective processes of reabsorption by which escape of water, salts and diffusible nutrients essential for survival is prevented are distributed among the different segments of the tubules. These are the processes which are finely adjusted to serve the varying excretory requirements of the body as a whole. By chemical rather than by nervous messages, tubule cells are informed of small changes in the composition of the blood, by mechanisms, as yet beyond description, their response is so discriminatingly effective that the narrow optimal range of its variations is preserved.

Tubule cells also excrete. The demonstration of this capacity in the mammalian kidney is as yet limited largely to the excretion of substances which are not normal products of metabolism or constituents of the normal diet. Its mechanism is wholly obscure. It may be that future work will show that this capacity is more important in normal urine formation than present knowledge indicates. If so revisions of current belief will be necessary.

The information upon which these statements are based is significant in that from it we gain clearer definition of future problems and more secure foundations of interpretations.

## THE NATURE OF THE VISUAL PROCESS

*Harvey Lecture, October 21, 1937*

SELIG HECHT

Professor of Biophysics Columbia University New York

## I HISTORICAL ORIENTATION

THIRTY YEARS ago, about the time the Harvey Society was founded, physiologists were rapidly losing interest in the study of vision and photoreception. During the fifty years preceding that time, physiology had been turbulent with the quarrel between Hering and Helmholtz and their followers. This vigorous and frequently acrimonious debate had served its purpose of stimulating research and clarifying the ideas involved. But with the death of Helmholtz and Hering, the argument as well as the patience of physiologists wore itself out, and by 1915 even the efforts of Ladd-Franklin to revive it in this country aroused only an amused or bored tolerance on the part of physiologists. The quarrel seemed far from the center of physiology, and our imagination and interest could not be fired by the problems. It is no wonder then that during the existence of the Harvey Society no one before today has lectured to it on the physiology of vision. Before progress could again be made in this field, there had to be a period of quiescence out of which was to come a new orientation.

The historical quarrel had been about the facts of color vision and about its theoretical basis. The new impulse, which twenty years ago began to revivify the study of vision, came from an entirely new quarter. Physiology as a whole was just beginning to feel the powerful influence of the rapidly growing science of physical chemistry, and the moribund subject of vision shared in the general stimulation which resulted.

Its special activating agent was that portion of physical chemistry known as photochemistry. This was a new science, which had just grown up from its early beginnings by Grotthus, Draper, Bunsen, and Roscoe, through its adolescent period by Luther and Weigert, and had only just received its coming of age recognition in the form of

Einstein's Photochemical Equivalence Law In 1911 Weigert had summed up its available knowledge in a thin volume in German and Sheppard in 1914 had organized the field in English in a more bulky monograph Here then was knowledge which could be drawn on for an understanding of the nature of vision and photoreception

New impulses are never completely new, and what at first appears as a break with traditionally accepted views, often turns out to be really in the tradition, the connection having become obscured in the period preceding the break About a hundred years ago, when Niépce and Daguerre discovered how to fix an image produced photochemically, Moser (1842) had suggested that the action of light on the retina was similar to the action of light on photosensitive materials generally Such a photochemical idea of retinal action was accepted by many physiologists It received dramatic confirmation by Boll's discovery in 1876 of a light sensitive substance in the retina and by Kuhne's extraction of this substance, visual purple, a year later

Kuhne's (1879) beautiful researches with visual purple raised hopes for a speedy solution of the problems of vision But these hopes were quickly disappointed, and that for two reasons In the first place, neither visual purple nor any similarly sensitive material could be extracted from the cones, and the cones are the elements which mediate color vision and most other visual functions under ordinary conditions In the second place, the behavior of visual purple did not seem easily to be related to the specific properties of vision as they were then known Therefore, in the excitement of the color vision debate, visual purple and photochemical notions were relegated to the background

The new interest in photochemistry brought these ideas back, but it was not visual purple which led to the photochemical study of vision, but precisely the reverse It was the developments in photochemistry which were first applied to the solution of visual problems, and these later brought a renewed interest in visual purple

Perhaps the first efforts to apply concrete photochemical ideas to vision and photoreception were made by Lasareff in 1913, and independently a little later by Putter (1918) and by myself (Hecht, 1918) With these as beginnings, a new interest has developed and has grown into an increasingly larger volume of researches and ideas, ripe for evaluation and synthesis My virtue as speaker this evening is merely that the other two pioneers have left the field, while I have persisted

## II POINT OF VIEW

Before presenting some of these researches, it is well to formulate the point of view which underlies them, since it must form the background of the story. A process, such as vision in man, represents a complicated series of events. It is not only the photoreceptor process itself which takes place in the outer end organs, but the nerve impulses which come from them, and which, when joined by other impulses, then pass through the various pathways to be transmitted, amplified, and perhaps altered, until the final results at the cortex are achieved. Nor is the photosensory system of other animals much simpler. The receptor system is there, impulses are involved, ganglia have to be passed, and reflexes have to be initiated.

Since all these elements enter into the end result, they surely influence its characteristics to some extent. The question is to what extent? And the answer can be secured only by experiment. Our own idea has been that no matter what enters in the chain of events, the ultimate place of origin of the impulses which pass along the optic tracts is in the initial action of light on the receptor cells in the sense organ. Therefore, for a number of years we have measured the different functions of vision and photoreception in man and other animals to ascertain how their quantitative properties depend on the characteristics of these very first reactions which must take place between light and the sensitive elements.

Such a viewpoint has become justified by experience. In addition, there are physiological considerations which render it not only acceptable, but compelling. For example, Adrian (1928) has studied the behavior of preparations which are combinations of sense organ and nerve, and he found in all cases that the nerve is far more rapidly acting and far less fatigable than the sense organ. Therefore, what the combination of the two transmits is determined by the events in the sense organ and not in the nerve.

The human eye is a complicated sense organ, and it might seem that the information gained about it would be both complicated and special, and would contribute little toward a basic understanding of the nature of the photoreceptor process. For my own part, I accepted this idea at the beginning and began work with more lowly animals such as the ascidian and the clam. However, as the work progressed, it became apparent that the human eye is just as capable of yielding fundamental



information, provided one has the wit to recognize it. To find the general implications of human vision, it is only necessary to ascertain and to evaluate those of its properties which are special. Once understood, these special conditions may be eliminated experimentally, or measured and corrected for. In the last few years there has therefore accumulated a considerable amount of new and precise data recording the quantitative properties of various visual functions. In addition, many of the older measurements have been freshly examined, and the whole field has achieved a form and unity which it did not have a generation ago. It is my purpose to present only one facet of this pattern for your examination in detail, and to sketch in the rest of it in outline only.

The function to be considered in detail deals with the recognition of flicker. The reason for its choice is first, that it illustrates the essentials of the process as a whole, and second, that its investigation and understanding has in large measure occurred in our own laboratory.

### III RODS AND CONES

Two things have to be made clear before it can be considered that we have begun to understand the visual process in the retina. One is the relation of the measurements of visual function to those morphological elements in the retina which are concerned with receiving the light, and the other is the more intimate chemical relation between the absorbed light and the photosensitive substances within the retinal elements. We shall consider the morphological basis before presenting the measurements, and deal with the chemical basis afterwards.

The retinal elements concerned with vision are the rods and cones, whose relative distribution and separate function make it necessary to treat the vertebrate eye not as a single sense organ, but as a double one. This is the duplicity theory which was first proposed by Max Schultze in 1866. It was completely ignored for a generation, and gained recognition only when it was independently developed by Parinaud in 1881 and by von Kries at about the same time. In its essentials the duplicity idea supposes that the retinal cones are the receptors for color vision and for vision at high intensities, while the rods are the general receptors for light regardless of color, and function best at low intensities.

In the human eye, the center of the retina is occupied exclusively by cones, while the rest of the retina contains rods and cones, with rods increasingly predominant toward the periphery. There is a central area

whose diameter is very nearly  $1.5^\circ$  which is completely rod-free, while a slightly larger area,  $2^\circ$  in diameter, contains so few rods that it may be considered practically rod-free (Schultze, 1866, Rochon-Duvigneaud, 1907, Wolfrum, quoted by Dieter, 1924, Østerberg, 1935). As a result, vision at high illuminations is color vision and is most efficiently carried on with the center of the retina, while at low illuminations vision is colorless and is most effective in the periphery.

The necessity for understanding this morphologically and functionally dual nature of the human eye is aptly illustrated in the history and data of flicker. The reason is that this field of knowledge has had a particularly rapid development in the last few years, and the steps in its organization and understanding are easily available.

#### IV THE PROBLEM OF FLICKER

When the light from an object is regularly interrupted, the resulting appearance of flicker depends for its magnitude on the frequency of the interruptions. When the frequency is low, the contrast between light and dark is great, but as the frequency is increased, the contrast becomes less, and the flicker can disappear completely when the frequency of interruptions is made sufficiently high. The precise point at which flicker disappears is known as the critical fusion frequency, and may be determined with considerable accuracy. As a result, its value has been shown to depend on a variety of conditions.

The most basic factor which controls the critical frequency is the intensity. Though the dependence of the critical frequency on illumination was recognized over one hundred years ago by Plateau (1829) and is evident from the work of Emsmann (1854) and of Nichols (1884), it was only forty-five years ago that Ferry (1892) formulated what has since become known as the Ferry-Porter Law, namely, that the critical frequency is proportional to the logarithm of the illumination intensity. Ferry's published measurements support this formulation only in the most general way, but the later data of Porter (1902) are adequate for its statement. Porter's work was corroborated by Kennelly and Whiting (1907), by Ives (1912), and by Luckiesh (1914).

Porter's measurements did more than establish the validity of the logarithmic relation. They pointed distinctly toward the separate function of the rods and cones in flicker. When his data of critical fusion frequency—as cycles of light and dark per second—are plotted against

the logarithm of the intensity, they fall on *two* straight lines instead of one. The slope of the line at low intensities is 1.56, while that of the line at high intensities is 12.4, and their interpretation as rod function and cone function respectively is obvious in terms of the duplicity theory. Porter's findings were confirmed by Ives (1912), whose data for different parts of the spectrum also show a dual logarithmic relation. However, the slope of the straight lines and their point of intersection seem to vary with the wave-length of the light, the upper and lower limbs of the relationship varying in different ways. In addition, Ives found the extraordinary fact that for blue light the low intensity line becomes horizontal.

These peculiarities were difficult to reconcile with the simple duplicity interpretation, and this difficulty was emphasized by Allen (1919, 1926) who drew through his measurements about five short straight lines of different slope instead of the usual two. The data presented by Allen do not justify this treatment, the points appear to lie on a continuously curving line, but their continuity is obscured by Allen's neglect of such experimental precautions as fixation, the presence of an adequate surround, and the proper adaptation to each intensity. The work of Lythgoe and Tansley (1929), which took all these precautions, distinctly gives no support to Allen's multiplicity of straight lines.

Lythgoe and Tansley's measurements confirm the logarithmic relation of intensity to fusion frequency, but Lythgoe and Tansley attach no importance to its strict formulation as done by Ferry, by Porter, and by Ives, and consider that their data agree only under certain conditions with the linear relation of critical frequency to  $\log I$ . The same may be said about the measurements of Granit and Harper (1930), who found that for a range of about 1 to 1000 in intensity, the critical frequency is very nearly directly proportional to the logarithm of the intensity. For higher intensities the relationship does not hold, and the curve of frequency against  $\log I$  tends to become horizontal, as already found by Grunbaum (1898).

One striking thing appeared in the work of Lythgoe and Tansley. Ives had found that for blue light the lower limb of his data is horizontal, and in this he had been confirmed by Allen. Ives thought that this was a special property of blue light. However, Lythgoe and Tansley recorded that when measurements are made with a retinal area  $10^\circ$  off-center, the lower portion of the data tends to be horizontal even for white light, and they correctly interpreted this horizontal portion as

due to the appearance of rod function in the periphery at low intensities

The confusion in flicker measurements which caused Lythgoe and Tansley to explore the influence of fixation, surround, and adaptation on critical frequency, also prompted us independently to study flicker, this, and the fact that none of the measurements existing at the time, nor those published during our investigations, covered a range of intensities sufficient to define the relation between critical frequency and intensity over the functional range of the eye. Since then, we have measured this relation for different portions of the retina, for different sizes of field and for different colors, for as large a range of illuminations as possible, and under such conditions of fixation and surrounding illumination as to render the data reproducible and definitive. As a result the confusion has disappeared, and the conflicting data have become understandable and consistent with other visual knowledge.

#### V CENTRAL AND PERIPHERAL MEASUREMENTS

If the separation of rod and cone function first suggested by Porter's data is correct, it should be possible to isolate these two functions by using the known structure of the retina. The central  $2^\circ$  of the retina is practically rod-free. Therefore, the relation between fusion frequency and intensity, if measured with central areas smaller than  $2^\circ$  in diameter, should be a continuous function representing cones, whereas with larger areas or with similar small areas outside the fovea, the relation should show a duplex character illustrative of the predominant working of rods at low intensities, and of cones at high intensities.

The measurements of Hecht and Verrijp (1933*b*) with a small field located centrally and peripherally show this expectation to be correct. Fig. 1 shows two sets of measurements made several years apart (Hecht and Verrijp, 1933*b*, Hecht and Smith, 1936) with a  $2^\circ$  field situated in the fovea. The data demonstrate that for the rod-free fovea there is one continuous relation between critical frequency and the logarithm of the intensity. The relationship is distinctly sigmoid, the S-shape being rather drawn out. In the middle range of intensities, the data lie with reasonable precision on a straight line and thus confirm Porter, Ives, and the other workers, even to the extent of having a slope of the same magnitude as found by them.

Below the middle range the data form a gentle curve which stops fairly abruptly when with central fixation the field appears uniform

even when the test area is extinguished. At the highest intensities the relation between critical frequency and  $\log I$  rapidly ceases to be linear. The curve flattens out, and, as with other visual functions such as intensity discrimination and visual acuity, remains flat provided the adaptation and surround are adequate.

Using the same sized field ( $2^\circ$  in diameter with a non-flickering  $10^\circ$  surround) we measured the relation between critical frequency and intensity at  $5^\circ$ ,  $15^\circ$ , and  $20^\circ$  from the center. The results are shown in Fig. 2, and are strikingly different from the central data in that they clearly fall into two parts. The first is at low intensities, where the critical frequency first rises with  $\log I$  and then reaches a maximum which is maintained approximately constant for about 1.5 logarithmic units. The total intensity range covered by this rise and plateau is about 3.5 logarithmic units. The second part also begins with a rise in critical frequency as  $\log I$  increases, and also terminates when the critical frequency reaches a maximum. The intensity range covered by the second part is about 4 logarithmic units. The same results obtain in whatever peripheral direction of the eye the measurements are made.

Since the central  $2^\circ$  field falls within the relatively rod-free area of the retina, the continuous nature of the data mark them as a function of the cones alone. The double nature of the peripheral measurements very likely represents rod function for the low intensity section, and cone function for the high intensity section. This is borne out by the increas-

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Fig. 1 Critical frequency and illumination. The data show a comparison for the same eye (S. H.) using central fixation and a  $2^\circ$  flickering field, between measurements made several years apart with a  $10^\circ$  surround (Hecht and Verrijp, 1933b) and with a  $30^\circ$  surround (Hecht and Smith, 1936).

Fig. 2 Relation between critical frequency and  $\log I$  for white light with a  $2^\circ$  field in four retinal locations: at the fovea, and at  $5^\circ$ ,  $15^\circ$ , and  $20^\circ$  above the fovea. The data are from Hecht and Verrijp (1933b). Due to an error in the original paper, the intensities have had to be multiplied by 40 to convert them correctly into those here given.

Fig. 3 Influence of the area of test field on the relation between critical frequency and  $\log I$  (Hecht and Smith, 1936).

Fig. 4 Area and the flicker relation. The  $\log I$  axis is the same for all the data. The numbers on the  $\log$  frequency axis to the left apply to the uppermost data only; the other data have been moved down in steps of 0.2 log unit in order to space them, and their precise position is given on the right. The curves are from equation (3) to be derived later, in which for the cone portions  $m=2$ ,  $n=2$ , and for the rod portions  $m=2$ ,  $n=1$ . Cf. Fig. 13 shown later.

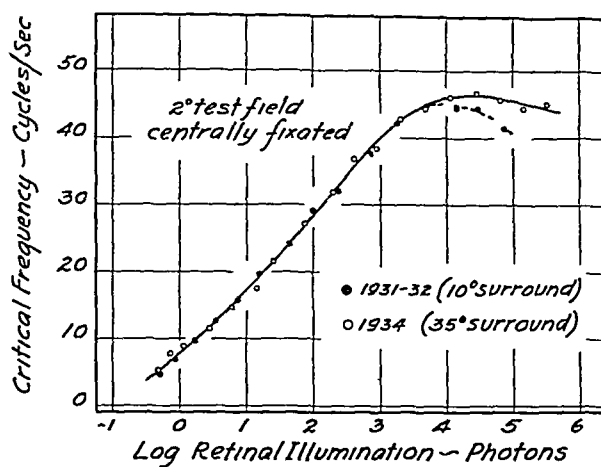


Fig 1

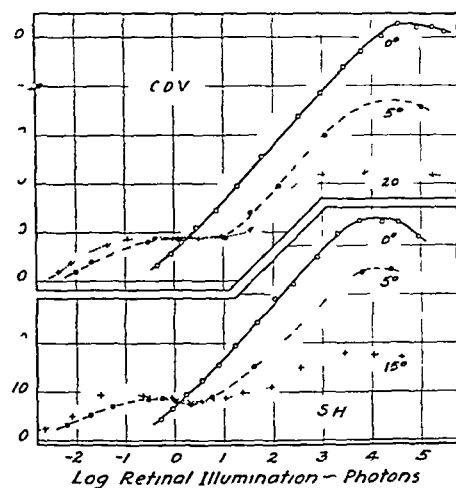


Fig 2

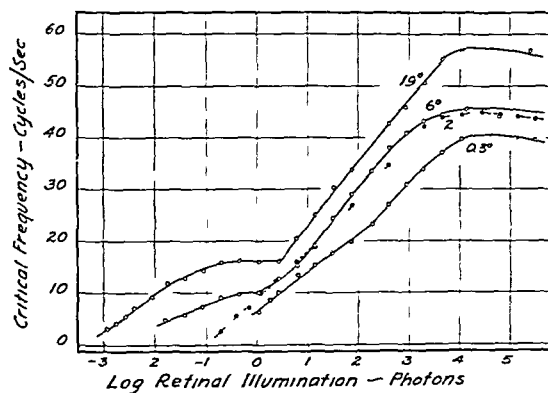


Fig 3

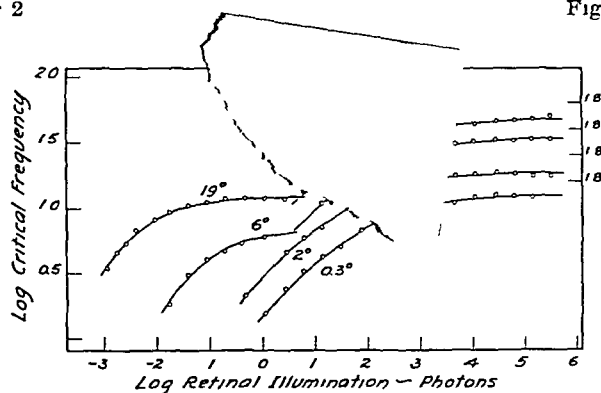


Fig 4

ing separation of the two sections as measurements are made farther and farther from the center the cone section shifts to higher intensities and the rod section to lower intensities, as would be expected from the increasing ratio of rods to cones in these regions

## VI AREA AND FLICKER

We have also measured the relation between critical fusion frequency and intensity for four centrally located areas  $0.3^\circ$ ,  $2^\circ$ ,  $6^\circ$ , and  $19^\circ$  in diameter, and our measurements (Hecht and Smith, 1936) confirm these conclusions. The data for E. L. S. are in Fig. 3, and, as expected, those for  $6^\circ$  and  $19^\circ$  break sharply into two sections while the  $2^\circ$  and  $0.3^\circ$  fields show only one continuous function. The slight bend in the latter data need not concern us here, it is certain that the bend is not due to a slight admixture of rods.

Fig. 4 presents the data of S. H. plotted as the logarithm of the critical frequency against the logarithm of the intensity. This type of plot shows more strikingly the phenomena already described. In spite of the irregularity in the  $0.3^\circ$  data, a single curve describes the measurements fairly well. The same single curve is even more expressive of the  $2^\circ$  data, and it is also drawn through the cone portions of the  $19^\circ$  and  $6^\circ$  data.

The rod sections of  $19^\circ$  and  $6^\circ$  require a slightly different curve which is the same for the two fields. It is worth emphasizing that the rod sections of the two large fields have the same curve drawn through them. While this is not clearly seen in an ordinary graph of critical fusion frequency against  $\log I$ , it becomes plain in the log-log plot of Fig. 4. This is because on a log-log plot of this kind the shape of the curve relating critical frequency and intensity is invariant, and uninfluenced either by the intensity units or by the absolute values of the critical frequency, since these merely shift the position of the curve on the two axes. The identity of the curves for  $19^\circ$  and  $6^\circ$  shows that the difference between them is not basic, but merely represents a change in one of the constants in the equation which describes them.

Exactly the same is true for any systematic differences which the cone data show. Fundamentally the systems in the rods and cones which determine the relation between critical frequency and intensity remain the same regardless of area. Only the parameters are altered by changing the area. This has finally been recognized by those investi-

gators who are interested in studying the influence of various factors on visual functions. For example, Smith (1936), who was concerned with synaptic and other nervous influences on intensity discrimination, has found that the basic intensity discrimination relation remains unaltered, and that the best way to describe these various nervous influences is to record their effects on the parameters of the fundamental equations (Hecht, 1935) for intensity discrimination. The same thing should be possible with flicker.

## VII SPECTRAL MEASUREMENTS

In order to confirm the identification of the two sections shown by the measurements which include the periphery, we have studied the relation of critical frequency to intensity in different parts of the spectrum. The reason for such an investigation, and the results to be expected from it, may be understood by an examination of Fig. 5 which shows the sensibilities in the spectrum of the cone system and the rod system. The data record the relative energy at each wave-length required to elicit a minimal visual effect by each system. Each curve is accurate by itself, but the vertical separation between the two is arbitrary. This separation varies with the position on the retina, but with all positions it is true at the red end of the spectrum that there is very little separation between the rod curve and the cone curve, and that the cone curve is always above the rod curve.

Fig. 5 tells us that beginning at the lowest energy level and moving vertically along any ordinate, no visual effect is produced until the rod curve is reached. The resulting sensation will be colorless and will continue to be controlled by the rods as the energy increases until the cone curve is reached, at which point one will begin to recognize color. The significant point of Fig. 5 is that this photochromatic, rod-cone interval varies with the wave-length, being very small in the red, and large in the blue. This is indeed represented by the well known fact that the colorless and color thresholds of the eye are very nearly coincident in the red, but are widely different in the blue (Charpentier, 1880).

The result of all this is that the relation between critical frequency and illumination when measured with red light should show little or no rod section, while with blue and green lights the rod section should be large, for intermediate parts of the spectrum the rod section should



be intermediate in extent. Since preliminary investigation (Hecht and Verrijp, 1933a) showed these expectations to be correct, we measured in detail (Hecht and Shlaer, 1936) the relation between intensity and critical frequency for different parts of the spectrum with a circular test field  $19^\circ$  in diameter, surrounded by a non-flickering area  $35^\circ$  in diameter.

The information conveyed by the measurements can best be understood from their graphic representation. As Fig. 6 shows, the data break into two sections. The high intensity portions, identified with cone function, fall together for all the colors. The low intensity sections, identified with rod function, are spread out much as expected, and extend to lower and lower intensities with decreasing wave-length.

Fig. 6 resolves the mystery of Ives' old measurements showing that the low intensity portions of critical frequency data which he found for different parts of the spectrum may be represented by straight lines which differ in slope, the red being steepest and the violet being prac-

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Fig. 5 Relation between wave-length and relative energy required to produce a specific visual effect at high and at low illuminations. The lower data are from Hecht and Williams (1922) and represent the relative energy required to produce a barely perceptible brightness after prolonged dark adaptation. The upper data are from Hyde, Forsythe and Cady (1918) and give the relative energy to produce a given high brightness, using only the fovea. The two curves are each accurately drawn from their separate data. Their vertical separation, however, has been arbitrarily arranged so that they are nearly coincident at the red end of the spectrum, this is a graphic expression of the fact that the colorless and color thresholds of the eye are nearly identical in the red.

Fig. 6 Critical frequency and  $\log I$  for different parts of the spectrum for the eye of S. H. (Hecht and Shlaer, 1936)

Fig. 7 Critical frequency and intensity for different spectral regions for the eye of

S. S. (Hecht and Shlaer, 1936) plotted as log frequency against log intensity. The numbers on the ordinates to the left apply to the topmost data, for convenience, the others have been moved down in steps of 0.2 log unit, and their exact positions are indicated to the right. The curves are from equation (3) to be derived presently, in which for the cone portions  $m = n = 2$ , and for the rod portions  $m = 2, n = 1$ .

Fig. 8 The relation between critical fusion frequency and intensity for four species of fish.  $L$  is for the sunfish *Lepomis* (Wolf and Zerrahn-Wolf, 1936),  $X$  is for the sword tail, *Xiphophorus*,  $P$  for the black platy, *Platypoecilus*, and  $B$  for the Black Helleri which is a complicated cross between the sword tail and the black platy (Crozier, Wolf, and Zerrahn-Wolf, 1937). The ordinates apply to the *Lepomis* data, the other measurements have been lowered 0.5, 1.0, and 1.5 log units respectively merely to keep them apart. The curves through the measurements are from equation (3) with the values of  $m$  and  $n$  as given for each species.

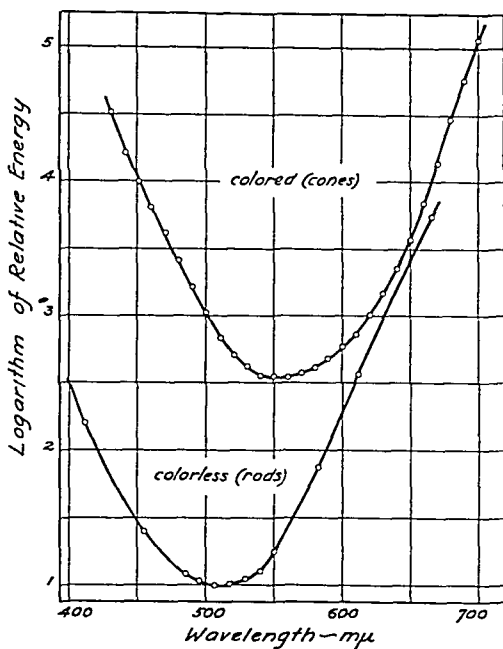


Fig 5

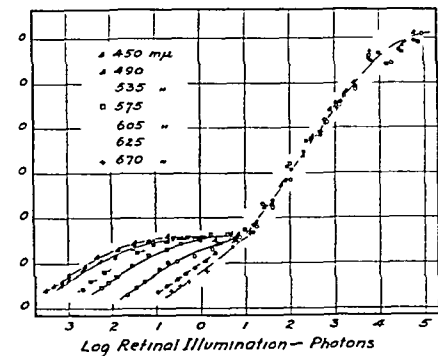


Fig 6

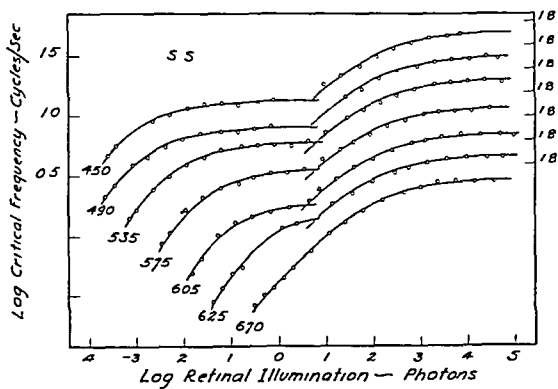


Fig 7

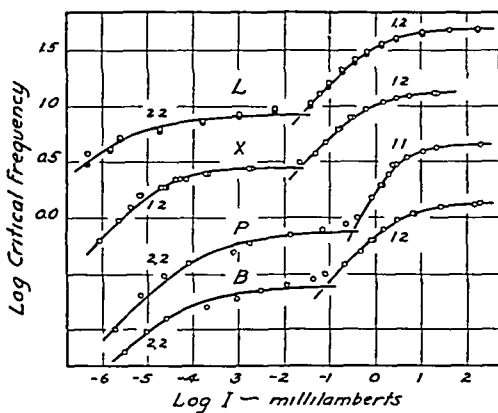


Fig 8

tically horizontal. It is apparent in Fig. 6 that for short stretches near the rod-cone transition, straight lines can be drawn through the rod data, showing different slopes for the different wave-lengths.

The real phenomenon, however, is something quite different. It is that the separation of rod and cone sections as a whole increases as the wave-length decreases. This is shown strikingly by Fig. 7 in which the data of S. S. are plotted as the logarithm of the critical frequency against the logarithm of the intensity. The data for 670 m $\mu$  fall on a single, continuous curve, whereas the data for all other parts of the spectrum are best described by two separate curves. The transition between the two portions is quite sharp for all but the blue and violet data. The high-intensity cone curve is in the same position for all colors, and the only effect of changing the spectral composition of the light is to shift the position of the low-intensity rod curve along the intensity axis, without in the least changing its form.

The identification of rod and cone function is borne out by subjective observation. At low intensities and below the critical fusion frequency the flicker is distinctly located in the peripheral portion of this 19° field so that the field resembles a flickering doughnut, and the last appearance of flicker is always in the periphery. With increasing intensity the first sign of approaching cone function is the appearance of color in the field, which becomes identifiable with certainty about 0.5 log unit below the actual inflection point of the measurements.

At the intensities around the transition, two separate loci of flicker are very often apparent near the critical frequency—one in the periphery, and the other in the center. At intensities higher than the transition intensity but near it, flicker usually persists longest in the center, but beyond these intensities the last trace of flicker may be in any part of the field. Obviously the rods determine the low intensity section and the cones the high intensity section.

## VIII. OTHER VERTEBRATES

Other vertebrates such as the bony fishes are known to have rods and cones (Schultze, 1866, Wunder, 1925), and Bauer (1910, 1911) and von Frisch (1925) found that they show the Purkinje phenomenon, indicating that their high and low intensity visibility curves differ in position on the spectrum. Using the method of moving stripes which we developed for work with animals other than man, Grundfest (1932)

actually determined the two visibility curves for the sunfish *Lepomis*, and found the low intensity maximum at  $540\text{ m}\mu$  and the high intensity maximum about  $45\text{ m}\mu$  farther in the red. It is therefore to be expected that the visual functions of fish should also show a double form representing rod and cone behavior.

This is true. Wolf and Zerrahn-Wolf (1936), using the moving stripe method, have made critical frequency measurements with the same species of sunfish used by Grundfest. Just as Grundfest found two visibility curves, so Wolf and Zerrahn-Wolf find two limbs to the flicker data, indicating separate rod and cone function. As Fig. 8 shows, the intensity separation of the two limbs is more than 4 log units, the main rod section being almost impossible to measure because it lies below the threshold of human vision. Very recently Crozier, Wolf, and Zerrahn-Wolf (1937) have reported flicker measurements with three other species of fish. The data are all given in Fig. 8, from which it is apparent that the separateness of rod and cone behavior in the visual functions of fish is amply established.

## IX OTHER VISUAL FUNCTIONS

Out of the detailed study of flicker there have come two characteristics of the dependence of visual function on intensity. One is the separateness of rod and cone behavior corresponding to expectation from the duplicity theory. The other is the increase in effectiveness of visual function with the increase in intensity to which the eye is adapted. In each system the increase is at first rapid and gradually reaches a maximum which is maintained. Both these characteristics are evident in all other visual functions which have been studied in relation to intensity. I shall illustrate this with visual acuity and intensity discrimination, though it is apparent in other functions as well (*cf.* Hecht, 1937).

Fig. 9 shows Koenig's (1897) measurements of the relation between visual acuity and the intensity to which the eye is adapted. Visual acuity is defined as the reciprocal of the angular distance which must separate two contours in order that they may be recognized as discrete, the unit of separation being a minute of arc. The dichotomy of the data in Fig. 9 is startlingly clear. With red light there is one continuous function which is obviously that of the cones. With white, green, and blue lights there are two relationships,—one at high intensities and

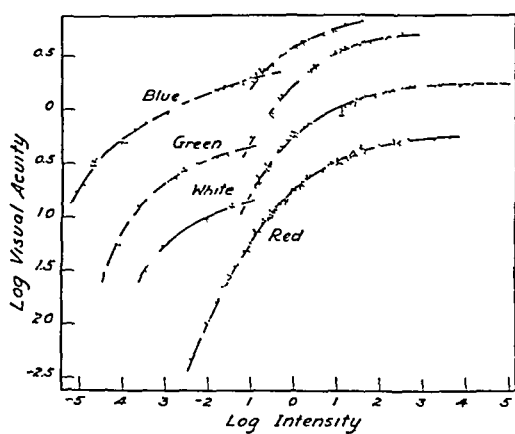


Fig 9

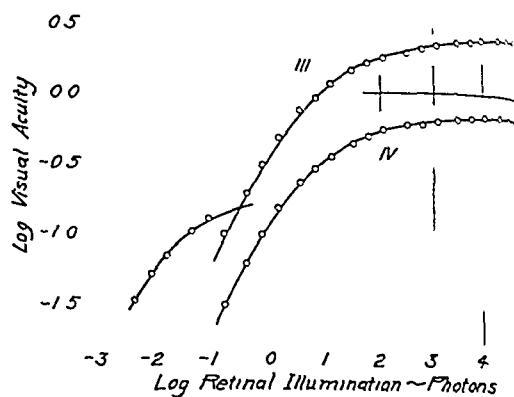


Fig 10

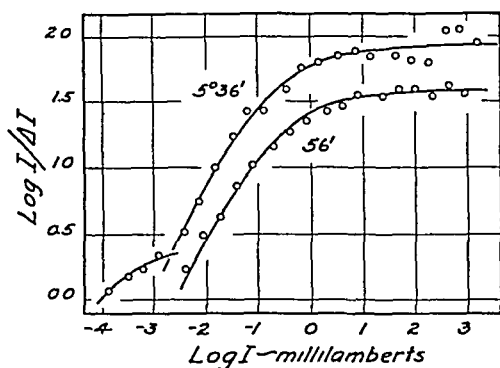


Fig 11

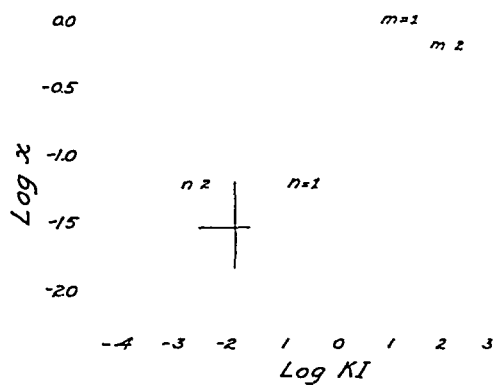


Fig 13

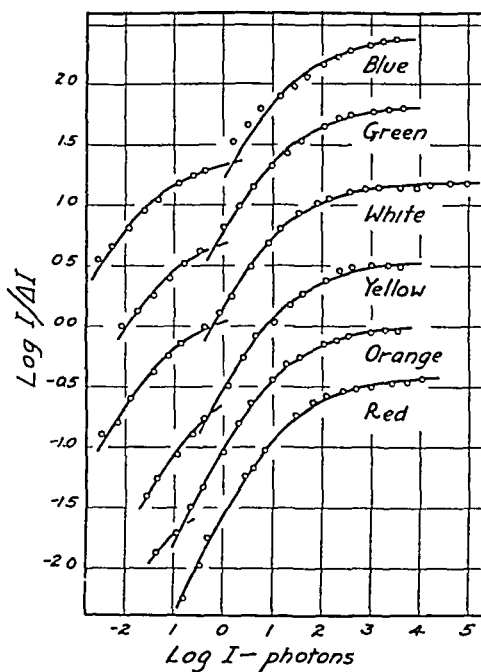


Fig 12

the other at low intensities. The high intensity limb for all the colors is the same as for red, and thus represents cone function, by the same token, the similarity of the low intensity portion for blue, green, and white, and its complete absence in the red, mark it as the expression of rod function. In particular, note the position on the intensity axis and the relative size of the rod portions for blue, green, and white. The blue section is largest, the green next, the white next, and the red is non-existent, just as we found with flicker.

Shlaer has very recently (1937) made visual acuity measurements with white light in which the function was deliberately confined to the rod-free center of the retina. As was to be expected, he found that under such circumstances the relationship between visual acuity and

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Fig 9 Visual acuity and illumination for different colors (Koenig, 1897). The intensity axis is the same for all the colors. The numbers on the visual acuity axis apply only to the data for white light. For convenience in showing the data, the red measurements have been displaced downward 0.5 log unit, the green, 0.5 log unit upward, the blue, 1 log unit upward. The separation of the data into two sections needs no emphasis.

Fig 10 Visual acuity as related to intensity for two observers (Shlaer, 1937). In each case the cone measurements were specifically confined to the fovea. The curves through the data are from equation (3) with  $m = n = 2$  for the cones, and  $m = 2, n = 1$  for the low intensity rod section.

Fig 11 The relation between intensity discrimination and intensity with different retinal areas and with white light (Steinhardt, 1936). The lower data for an area approximately  $1^\circ$  in diameter show only cone function and are described by equation (3) where  $m = n = 2$ . The upper data with a much larger area show both rod and cone function. Here too the cone section is described by equation (3) with  $m = n = 2$ , while the rod data are too few for critical determination, the curve through them has the same values of  $m$  and  $n$  as the cone section.

Fig 12 Intensity discrimination at different intensities for different parts of the spectrum. The ordinates are correct for the measurements with white light, those for green and blue have been raised 0.5 and 1.0 log units respectively while those for yellow, orange, and red have been lowered 0.5, 1.0, and 1.5 log units respectively merely to separate the points. For red the data are continuous and represent one functional system only, the cones. For the other colors a second system, the rods, becomes more evident at low intensities as the color moves toward the blue. As usual in visual measurements, white light behaves much as yellow light. The curves are from equation (3) with  $m = n = 2$  for the cone section, the rod section is also best described by the same values. The discrepancy near the transition between rods and cones for blue light shows up frequently with blue light measurements of other visual functions, cf Fig 7 for example.

Fig 13 The steady state equation (3) plotted when  $m$  and  $n$  are each 1 and 2. Because of the log plot the shape of the curves remains constant regardless of the values of  $K$  and  $a$ .

intensity is continuous and single, whereas similar measurements including the periphery show the usual double relationship. His data are shown in Fig. 10.

The increase in visual acuity which the eye shows with rising intensities has been known since Mayer first investigated it in 1754. What Koenig's measurements show in addition is that this increase is true for both rods and cones, and that the rate of increase slows up for each section. Indeed, Shlaer (1937) found that at intensities ten and even a hundred times higher than those attained by Koenig, visual acuity remains constant at a maximum value depending on the test object and on the pupil size.

Intensity discrimination shows precisely the same two properties as do visual acuity and flicker. If  $I$  and  $I + \Delta I$  are two intensities which can just be recognized by the eye as differing in brightness, then the fraction  $I/\Delta I$  is a direct measure of intensity discrimination. When the eye can tell only large differences in brightness, its intensity discrimination is poor and the fraction  $I/\Delta I$  is small, whereas when the perceptible difference  $\Delta I$  is slight, the capacity for intensity discrimination is good, and the fraction  $I/\Delta I$  will be large.

Intensity discrimination has been measured by Aubert (1865), by Koenig and Brodhun (1888), by Blanchard (1918), and others. Since I have already reviewed the extensive data on this subject (Hecht, 1935, 1937), it is unnecessary to go into it here; I shall therefore confine myself to two examples, chosen to illustrate the critical points involved. Steinhardt (1936) working in our laboratory was able to show that when intensity discrimination is measured at different intensities with white light, the results depend on the retinal location of the measuring area. With centrally-fixated test areas larger than  $2^\circ$ , his measurements without exception fall on a double curve showing rod and cone function, while for smaller areas they always form single curves like those for flicker and visual acuity under the same circumstances. Fig. 11 shows two examples of his measurements, one with a test field  $56'$  in diameter, and the other  $3^\circ 44'$  in diameter. The difference between them, and the meaning of the difference is obvious.

We (Hecht, Peskin, and Patt, 1937) have recently measured the relation between intensity discrimination and intensity for different parts of the spectrum. The results are shown in Fig. 12, and it is unnecessary to comment on them at length. They show essentially what

flicker and visual acuity showed, namely that there are two visual systems which seem to operate separately, and that for each system the visual function becomes better and more effective as the intensity is increased

It will not have escaped the reader that the way in which visual function and intensity are related is similar for the three properties here presented. This will become more evident when the nature of the receptor process has been discussed and quantitatively formulated

## X PHOTOCHEMISTRY AND VISION

In building a picture of the intimate chemical and physical events which underlie the visual process, we may start with the most general ideas about its nature. There are three things which must take place. First, there has to be a sensitive substance which absorbs light and is changed by it into one or more active products. Second, it is necessary to maintain a supply of this photosensitive material, otherwise it would be used up and the process would come to an end. These two processes may be called the primary light and primary dark reactions. Third, the active photoproducts of the primary light reaction must do something of which the end result is an impulse from the receptor cell. This is the secondary dark reaction.

These three requirements are the minimum essentials. The photo-receptor process itself is certainly more elaborate. Moreover, vision involves more than the photoreceptor process alone. Yet it is a fact of pertinent interest that the behavior of many visual functions may be formulated in quantitative detail in terms of these minimum essentials alone. Certainly the three visual functions of flicker recognition, intensity discrimination, and visual acuity may be described in this way.

Let us examine the properties of the simplest photochemical system which can be suggested as corresponding to the primary light and dark reactions. Consider a photosensitive substance  $S$  whose total initial concentration is  $a$ . Let light of intensity  $I$  shine on it, and as a result let there be produced the photoproducts  $P$ ,  $A$ , etc., whose concentrations at the moment  $t$  is given by  $x$ . The rate at which this primary light reaction  $S \rightarrow P + A$  goes will be proportional to the intensity and to the concentration  $(a-x)$  of sensitive material, this may be written

$$dx/dt = k_1 I (a-x)^m \quad (1)$$

where  $m$  is the order of the reaction, and  $k_1$  is a velocity constant which includes the absorption coefficient



Let us further suppose that some of these photoproducts  $P$ ,  $A$ , etc., can reunite by themselves or with the help of additional substances or energy to form again the sensitive material  $S$ . The velocity of this primary dark reaction  $S \leftarrow P + A$  will be proportional purely to the concentrations  $\nu$  of the photoproducts, this becomes

$$-d\nu/dt = k_2\nu^n \quad (2)$$

where  $n$  is the order of the reaction and  $k_2$  is its velocity constant

When such a system of two reactions is steadily exposed to light, corresponding to the adaptation of the eye to a given light intensity, the two reactions proceed simultaneously until their velocities become equal, and the system reaches a stationary state. Putting equations (1) and (2) equal to each other, and rearranging terms, we get

$$KI = \nu^n / (a - \nu)^m \quad (3)$$

where  $K = k_1/k_2$ . This is the equation of the photostationary state of the simple reversible photochemical system  $S \rightleftharpoons P + A$

Again it is necessary to emphasize that this formulation is too simple to correspond to what the photoreceptor process probably is (cf especially, Wald and Clark, 1937). But at the same time it is also important to state that the three visual functions presented in this paper all behave as if they were controlled by just such a simple system as represented by the stationary state equation (3). In fact, so close is the relation between equation and data that it is possible to determine from the measurements the numerical values of  $m$  and  $n$ .

Equation (3) may be studied by putting  $a$  equal to 100 per cent, and computing the values of  $KI$  for different values of  $\nu$  after  $n$  and  $m$  have been given values of 1 or 2. The results of such a series of computations are shown in Fig. 13. Because of the logarithmic plot, the curves keep their shapes regardless of the magnitudes of  $K$  or of the units in which  $a$  and  $\nu$  are measured. It is the values of  $m$  and  $n$  which determine the specific shapes and slopes of the curves.

It can be shown that at the stationary state produced by a given intensity  $I$  in such a photochemical system, the critical frequency is directly proportional to  $\nu$ , while the intensity discrimination  $I/\Delta I$  and the visual acuity are both directly proportional to  $\nu^n$ . It would take us too far afield to reproduce the derivations here, but they are simple and straightforward, and have been presented in detail elsewhere (Hecht, 1935, 1937). Because of this direct dependence of visual function on  $\nu$ , it is easy to compare the data with the curves of equation (3).

Actually the lines drawn through the measurements in Figs 4 and 7 for human flicker are the stationary state equation in which for the cones  $m = 2$  and  $n = 2$ , while for the rods  $m = 2$  and  $n = 1$ . Moreover, all the curves through the fish flicker data in Fig 8 are also from equation (3), for each curve the appropriate values of  $m$  and  $n$  are indicated in the figure

Exactly the same is true for the intensity discrimination data in Figs 11 and 12. The curves here are also that of equation (3). For the cone portion  $m = n = 2$  as for flicker. For the rod portion it is difficult to be certain, because in most cases the points are too few, but where the points are many  $m$  and  $n$  both seem to equal 2, and it is this equation which has been drawn through them.

Shlaer's visual acuity measurements in Fig 10 are also described by equation (3) of the stationary state. The curves in Fig 10 have  $m = n = 2$  for the cones, and  $m = 2$  and  $n = 1$  for the rods, just as we found for flicker. I have shown (Hecht, 1937) that Koenig's visual acuity data, when properly corrected for pupil area and efficiency, are also fitted by the same equation having the same values of  $m$  and  $n$  as Shlaer's for both cones and rods.

The conclusion from such numerical comparisons is clear. The quantitative properties of several major visual functions may be described with adequate fidelity in terms of the simplest theoretical assumptions about the photochemical and chemical reactions which must take place in the retinal elements.

## XI VISUAL PURPLE

The assumptions just made in the quantitative description of visual functions involve the existence of photosensitive substances in the rods and cones. What is actually known about such substances in the eye? For the cones no photosensitive substance is known, though repeated efforts have been made to extract one. There must be such a substance or several such substances, since the cone visibility curve undoubtedly represents their combined absorption spectrum. Evidently the sensitive materials are present in such high dilutions that their specific absorption in solution is masked by the other materials extracted with them.<sup>1</sup>

<sup>1</sup> Since this was written, Wald (1937) has reported that digitonin extracts of chick retina show the presence of two photolabile substances, one with an absorption maximum near 510  $m\mu$  and the other with a maximum near 570  $m\mu$ . The former is most probably visual purple, while the latter is the heretofore unknown cone photosensitive substance, which he calls iodopsin, but which may be called less formally visual violet. The chick retina is composed overwhelmingly of cones, though some rods are also present. Nevertheless, Wald's extract indicates a higher photometric density of visual purple than of visual violet even in this essentially cone retina.

For the rods, however, we have visual purple, which may be studied in the retina, or in solutions extracted from the retina

Kuhne (1879) could never separate visual purple from the proteins which were in its solutions. His studies on the destruction of visual purple by heat showed this process to have a high temperature coefficient much like that found later for the denaturation of proteins. This made it probable that visual purple itself is a protein, and we have now rendered it even more probable (Hecht, Chase, and Shlaer, 1937) by determining the molecular weight of visual purple. The value turns out to be about 800,000, which puts visual purple at about the same size as thyroglobulin (Heidelberger and Pedersen, 1935)

Visual purple is not a simple protein. Wald (1935*a*, 1935*b*, 1936) has found that on bleaching, visual purple yields a carotenoid, retinene, which slowly changes to vitamin A. This makes reasonable the relation between states of nutrition and vision, which has been known for centuries. Moreover his work has thus identified visual purple as a conjugated protein belonging to the carotenoid proteins, of which many are known as animal pigments, though none other than visual purple are sensitive to light.

Visual purple shows many properties which fit in with visual knowledge. Among these are its absorption spectrum which has its maximum at the same place as the rod visibility curve (Hecht and Williams, 1922). Also, visual purple even in solution can regenerate its color after having been bleached. Kuhne (1879) first recorded this sixty years ago, but since then no one was able to repeat his experiments though many investigators tried. Recently we (Hecht, Chase, Shlaer, and Haig, 1936) have found some of the conditions which make regeneration in solution possible, and have been able not only to confirm Kuhne completely but to measure the course of the regeneration reaction and to determine the absorption spectrum of the regenerated material. In addition Chase (1937) has found that for visual purple to regenerate in solution, another photosensitive substance present with it must also be bleached. This new photosensitive material is particularly sensitive to blue light and is different from visual purple.

Kuhne knew that *in the retina* visual purple may regenerate in two ways: directly from its photoproducts, and from newly supplied materials. Wald has confirmed and extended these findings, and has even shown that they clarify the behavior of rod dark adaptation which,

under certain conditions, shows two different courses (Winsor and Clark, 1936, Hecht, Haig, and Chase, 1937, Wald and Clark, 1937)

Much is expected from this direct photochemical and chemical approach to the study of vision, and it is to be hoped that the next few years will witness the fruition of these efforts

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## PROCEEDINGS OF ACADEMY MEETINGS

### STATED MEETINGS

DECEMBER 2—*The New York Academy of Medicine* Executive Session—a] Reading of the minutes, b] Election of Academy officers ¶ The ninety-first anniversary discourse was the first Joseph Collins Lecture and was delivered by Charles R. Stockard, Professor of Anatomy, Cornell University Medical College, on the subject, The Mechanisms Operating the Body as an Integrated Unit \* ¶ Report on election of members

DECEMBER 16—*The Harvey Society* (in affiliation with *The New York Academy of Medicine*) Third Lecture, The Functional Significance of the Lymphatic System, Dr. Cecil K. Drinker, Professor of Physiology, School of Public Health, Harvard University

### SECTION MEETINGS

DECEMBER 3—*Surgery* Reading of the minutes ¶ Presentation of cases—a] Lymphosarcoma of the jejunum, Frank Glenn, Discussion by William F. MacFee, John Douglas and Sidney Weintraub, b] 1 Hernia of jejunum and ileum through the transverse mesocolon, 2 Megacolon following the development of an aortic aneurysm, Harold J. Shelley, Discussion of the first case by John Douglas, Discussion of the second case by Edward Peterson, c] Carcinoma of the lower rectum Harold Brown Keyes, Discussion by William F. MacFee, d] Case illustrating paper on lymphogranuloma venereum, A. W. Martin Marino, e] Case illustrating paper on duodenal obstruction in the newborn, Walter Stenson ¶ Papers of the evening—1] The anorectal aspect of venereal lymphogranuloma, A. W. Martin Ma-

rino, Discussion by Frank C. Yeomans, b] Duodenal obstruction in the newborn A successful operation on a premature twin, Walter Stenson, Discussion by DeWitt Stetten, Jerome Leopold, Edward Donovan ¶ General discussion

DECEMBER 7—*Dermatology and Syphilology* Reading of the minutes ¶ Presentation of cases—a] Skin and cancer unit of the Post-Graduate Medical School, b] Miscellaneous cases ¶ Discussion of selected cases ¶ Executive session

DECEMBER 9—*New York Meeting of the Section of Pediatrics* Symposium on tumors of childhood presented by members of the staff of the Memorial Hospital Presentation of cases—a] A five year cure of a case of osteogenic sarcoma of the calcis, Norman L. Higinbotham, b] Hypertrophy of breast in a child, Joseph Farrow (by invitation), c] A case of hygroma of the neck, Robert L. Brown (by invitation) ¶ Papers of the evening—a] General considerations of cancer in children, Harold W. Dargeon, b] Malignant tumors of soft tissues in infancy and childhood, George T. Pack, c] Diagnosis and treatment of primary bone tumors in children, Bradley L. Coley, d] Malignant tumors of the head and neck in children, Hives E. Martin, e] Blood and lymph vessel tumors in children William L. Watson, f] Malignant lymphomatous tumors and leukemia in childhood, Lloyd F. Craver ¶ Discussion, James Ewing, Frank E. Adair

DECEMBER 14—*Neurology and Psychiatry* Papers of the evening—a] The attitude of the psychoneurotic toward scientific contraceptive advice, Jacob H. Friedman, Discussion, Israel Strauss, Clarence P. Oberndorf, b] Physiology of vision and quantitative visual test for

\* This was the first of two lectures on the general subject "The Interactions of the Endocrine and Nervous Systems"

localization of tumors of brain—a preliminary report, Charles A. Elsberg, Hyman Spotnitz (by invitation), Discussion, Selig Hecht, Ph.D., Professor of Biophysics, Columbia University (by invitation), John M. Wheeler, Felix Bernstein (by invitation), Richard Brickner, Hyman Spotnitz (by invitation), c] Observations on motor apraxia, Earl C. Chesher (by invitation), Discussion, Kurt Goldstein (by invitation)  
 \* Executive session

#### DECEMBER 15—*Genito-Urinary Surgery*

Reading of the minutes ¶ Presentation of cases—a] An induction motor suction pump for urological drainage, Harold E. Stedman (by invitation), b] A case of hydrocele testis, Stanley R. Woodruff, H. S. Rupert (by invitation) ¶ Paper of the evening—A clinical consideration of simple renal infections in the pregnant woman, Leon Herman, Craig W. Muckle, Philadelphia (by invitation) ¶ Discussion, Henry Dawson Furniss, Harbeck F. Halsted, George F. Hoch, Herbert F. Traut

#### DECEMBER 15—*Otolaryngology*

Reading of the minutes ¶ Presentation of cases—a] Malignant granuloma of the ethmoids, Alfred F. Hocker (by invitation) b] *Mesenchondroma* of the nose in an infant, Gervais W. McAuliffe ¶ Papers of the evening—a] Laryngo-fissure for removal of intrinsic carcinoma of the larynx (illustrated by colored motion pictures), Arthur Palmer (All of the foregoing contributions were from the otolaryngological staff of the New York Hospital, Cornell Medical College) b] A short report on the use of a new local anesthetic agent which gives prolonged analgesia, W. Wallace Morrison Discussion, Alexander F. Lallo (by invitation), Cresar Hirsch (by invitation) c] Otologenous cerebellar abscess, E. Miles Atkinson (by invitation), Discussion, Marvin F. Jones, J. E. F. King ¶ General discussion ¶ Executive session

#### DECEMBER 17—*Orthopedic Surgery*

Reading of the minutes ¶ Papers of the evening—

a] The relationship of orthopedic surgery to internal medicine, Harold I. Hyman (25 minutes), b] Subluxation of the cervical vertebrae, Barbara B. Stimson (30 minutes), c] Discussion, Alan DeForest Smith, Paul Swenson (by invitation), d] Resume of eighty operative cases of internal derangement of the knee joint, limited to damage to the semilunar cartilages, William Hadden Irish (25 minutes), e] Demonstration of a correcting spinal brace, John B. Byrne (15 minutes) ¶ Discussion

#### DECEMBER 20—*Ophthalmology*

Instructional hour—Diagnostic value of the fundus, Ernest F. Krug ¶ Slit lamp demonstration, Milton L. Berliner, Girolamo Boniccolto, Gordon M. Bruce ¶ Reading of the minutes ¶ Survey of eye clinics, N. Y. City, Robert R. M. McLaughlin ¶ Presentation of cases—a] Etiology and treatment of keratoconus, Arthur A. Knapp, b] Contrast media in orbital roentgenography, Murray A. Last ¶ Paper of the evening—Lymph spaces and lymphatics in and about the orbit, Oscar V. Batson (by invitation)

#### DECEMBER 21—*Medicine*

Reading of the minutes ¶ Papers of the evening—a] The nature and treatment of heart failure, Paul D. White, Boston (by invitation) Discussion, Lewis Fox Frissell, Henry S. Patterson, Harold J. Stewart, b] The value of the precordial electrocardiogram in coronary artery disease, Francis Clark Wood, Philadelphia (by invitation) Discussion, Arthur M. Master ¶ General discussion

#### DECEMBER 28—*Obstetrics and Gynecology*

Presentation of cases—a] Tuberculous pyonephrosis complicating pregnancy Nephrectomy, Norman Pleshette (by invitation), Discussion, Seymour F. Wilhelm b] Postpartum hemorrhage with uterine atony Hysterectomy, Harry Schneider (by invitation), Discussion, Harbeck Halsted ¶ Papers of the evening—a] The comparative value of pelvi-urodiagnosis and clinical pelvimetry in the course and progress of labor,

Samuel J Scadron, Emanuel Rappaport (by invitation), Discussion, William E Caldwell, Howard C Moloy (by invitation), Kyle B Steele (by invitation), Claude E Herton, b] Maternal intra-cranial hemorrhage complicating labor (with a report of three cases), H Leo Moskowitz (by invitation), Discussion, Emanuel D Friedman

#### AFFILIATED SOCIETIES

DECEMBER 15—*New York Section of the Society for Experimental Biology and Medicine* Red cell and reticulocyte counts in guinea pigs following exposure to low pressures, Albert S Gordon, William Kleinberg (introduced by Harry A Chrupper) ¶ Sensitization and antibody formation after the injection of tubercle bacilli, Jules Freund, J Casals (by invitation), Elizabeth Page Hosmer (by invitation) ¶ Direct effect of adrenal cortical hormone on blood pressure in shock induced by intestinal manipulation, W W Swingle, W M Parkins (by invitation), A R Taylor (by invitation), H W Hays (by invitation) ¶ Relation of carrier state to pneumococcal peritonitis in young children with the nephrotic syndrome, C M MacLeod, L E Farr (introduced by O F Avery) ¶ A simple, inexpensive method for concentrating serum under sterile conditions, William Thalhimer ¶ Experimental

tail exchange transfusions for reduction of anemia and the experimental use of an artificial kidney for that purpose, William Thalhimer ¶ The action of parasympathomimetic drugs on sympathetic synapses, Amedeo S Marrazzi (introduced by I Greenwald)

DECEMBER 20—*New York Roentgen Society* Presentation of interesting cases ¶ Papers of the evening—a] The application of the kymograph to body section radiography, Sherwood Moore, St Louis b] Cine-roentgenography, Maurice Lou Van de Maele, Brussels, Belgium, Presentation by William H Stewart ¶ Executive session

DECEMBER 23—*New York Pathological Society in affiliation with The New York Academy of Medicine* Case reports—a] Generalized arteriosclerosis with hypertrophy of the media and atypical hyaline degeneration affecting the intima media and adventitia, Charles T Olcott b] Epidermoid carcinoma of the breast, N Chandler Foot ¶ Papers of the evening—a] Studies on experimental hypertension, Charles G Child (by invitation) b] A study of myocardial hypertrophy of uncertain etiology in congestive heart failure Particular reference to the role of antecedent hypertension, Bernard I Kaplan (by invitation), Eugene Clark, Clarence E de la Chapelle ¶ Executive session

#### THE JOSEPH COLLINS LECTURES

The first and second lectures were delivered at the Academy on December 2 and December 8, 1937, at 8 30 o'clock by Dr Charles R Stockard, Professor of Anatomy, Cornell University Medical College, on the general subject, "The Interactions of the Endocrine and the Nervous Systems" ¶ Lecture No 1, Thursday evening, December 2,

"The Mechanism Operating the Body as an Integrated Unit" (This lecture also constituted the Anniversary Discourse of the Academy) ¶ Lecture No 2, Wednesday evening December 8, "Endocrine Changes and Modifications in Function and Behavior" Physicians and the public were invited to attend the Lectures

BULLETIN OF  
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FEBRUARY 1938

THE NATURE OF GLOMERULONEPHRITIS\*

GEORGE BAEHR

Associate in Pathology and Attending Physician The Mount Sinai Hospital

IT HAS become necessary to redefine glomerulonephritis, for old misconceptions have been revived in several recent pathological and clinical publications so that the subject is again in danger of being enveloped in the confusion which existed up to twenty-five years ago. The fault lies with some of our pathologists who lay undue weight upon cellular morphology and too little upon the whole picture of the disease. They exaggerate the significance of nonspecific cellular changes commonly seen postmortem in some of the renal glomeruli and regard them as lesser degrees of glomerulonephritis. This misinterpretation of a common post-mortem finding is analogous to the clinical error of diagnosing glomerulonephritis merely because of the presence of albumin and casts or of red blood cells in the urine.

By fixing kidneys in Helly's or Zenker's fluid and staining with the Mallory-Heidenhain azocarmine method, Bell<sup>1</sup> has demonstrated a minor degree of swelling of glomerular endothelium in many kidneys. It occurs at death in a variety of infections as well as in noninfectious diseases and, except in rare instances, is not associated with clinical manifestations of glomerulonephritis during life. Without clinical justification, he chooses

\* Delivered November 3, 1937 in the Tenth Annual Graduate Fortnight.

to call these glomerular changes "subclinical glomerulitis" and sees "transitions between this subclinical glomerulitis and acute glomerulonephritis" (Fig 1 A)

In other words, Bell conceives of glomerulonephritis as merely the advanced stage of glomerular changes which occur very commonly at death in varying diseases in which acute glomerulonephritis almost never occurs. Thus, he finds it in 41 per cent of cases of acute rheumatic endocarditis, a disease in which true glomerulonephritis is peculiarly rare.<sup>2</sup> In subacute bacterial endocarditis, he finds it in 79 per cent of the cases, although the absence of acute glomerulonephritis is a peculiar characteristic of the bacterial stage of this disease in contrast to bacteria-free cases.<sup>3</sup> Bell also describes it in 52.4 per cent of patients dying of puerperal sepsis, in 39.7 per cent of cases of pulmonary tuberculosis, in 50 per cent of lobar pneumonias and in 37.5 per cent of a miscellaneous variety of infections such as typhoid fever, septicemia, appendicitis, meningitis, diphtheria. He finds it in primary arterial hypertension, old healed valvular heart disease, pernicious anemia (four out of seven cases), carcinoma, subacute yellow atrophy of the liver. True clinical glomerulonephritis is observed so rarely during the course of these diseases that its occurrence may be regarded as an accidental coincidence. There is therefore no reason to believe that these very common minor glomerular changes bear any relationship to glomerulonephritis.

The unacceptable premise that these common glomerular alterations are a less intense variety of acute glomerulonephritis, leads Bell to an erroneous conclusion, "that acute glomerulonephritis is not a sharply circumscribed entity." It is the purpose of this paper to review some clinical and pathological experiences which demonstrate

(1) that acute glomerulonephritis (acute Bright's disease) is a sharply circumscribed entity,

(2) that it is part of a disease of the body as a whole,

(3) that its clinical manifestations can be related to characteristic pathological phenomena in various parts of the body,

(4) that the disease has a specific etiology and pathogenesis.

*The Acute Onset*—It is often insufficiently appreciated that acute diffuse glomerulonephritis *always* has an extraordinarily sudden onset. The disease actually begins with explosive suddenness. The glomeruli seem to be damaged simultaneously. In patients who die within a few weeks after the onset, all the glomerular lesions are in the identical stage

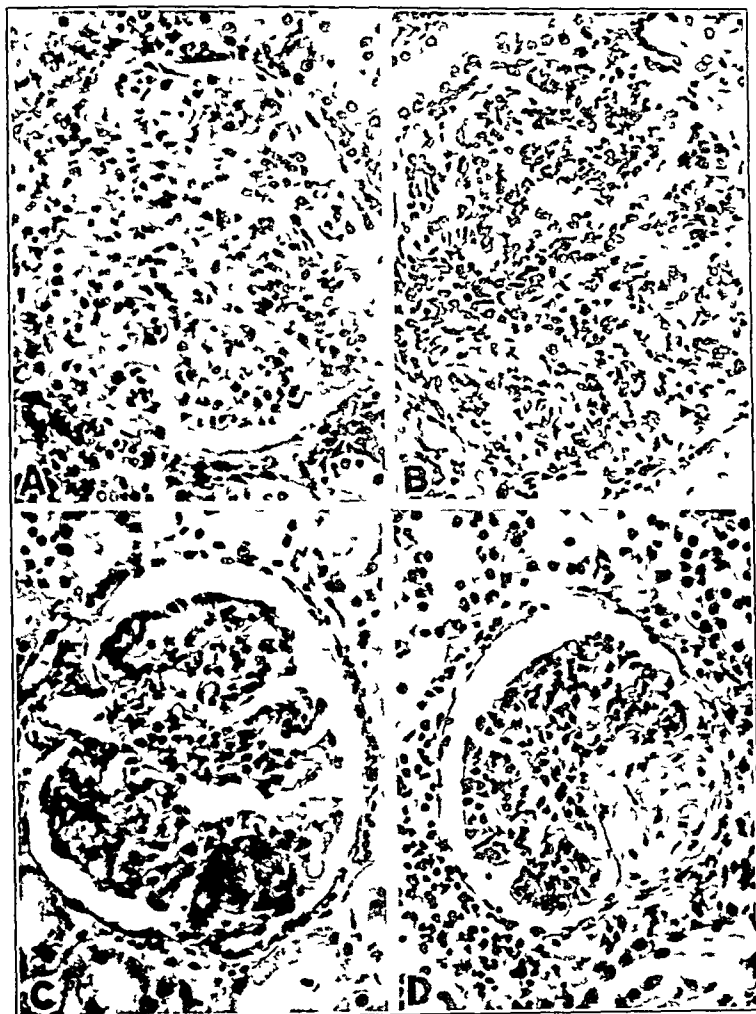


Fig 1 A, B, C, D

A Glomerular changes in acute bacterial (pneumococcus) endocarditis (Bell's glomerulitis) A common postmortem finding in many diseases, infectious, as well as non-infectious. Lesion in this case is probably due to direct action of bacteria or their toxins. Endothelial swelling of glomerular capillaries resembles glomerulonephritis, but the glomerular capillaries contain blood, the swelling affects only some of the glomeruli and the process is pathogenetically and clinically unrelated to true glomerulonephritis.

B Typical glomerular lesion in acute diffuse glomerulonephritis. Swelling and proliferation of glomerular endothelium, obliteration of Bowman's capsular space by maximum glomerular swelling, bloodless

capillary loops, beginning necrosis of loops. The process has affected all glomeruli throughout the kidney simultaneously.

C Fresh embolic glomerular lesion in subacute bacterial (*Streptococcus viridans*) endocarditis. The unaffected glomerular capillaries are normal anatomically and functionally.

D Old healed embolic glomerular lesion in subacute bacterial endocarditis. Only healed embolic lesions are found in cases which have become bacteria-free. In active cases with positive blood cultures and bacterial colonies in the vegetations, all stages of the process are usually to be seen from freshly embolized loops to completely healed lesions.

of development, although perhaps of varying severity (Fig 1 B)

This is in sharp contrast with focal glomerulonephritis or the embolic glomerular lesions of subacute bacterial endocarditis (Loehlein<sup>4</sup>, Baehr<sup>5</sup>) Embolic glomerular lesions recur in repeated showers over a period of months or even years In patients who die during the bacterial stage of subacute bacterial endocarditis, all stages of glomerular damage can be recognized from the fresh necrosis of glomerular loops, embolized within a few days, to old completely organized glomerular segments (Fig 1 C and D) Even in massive glomerular embolizations, many normal glomeruli can still be seen as well as normal portions of affected glomeruli For this reason, the embolic glomerular lesions of subacute bacterial endocarditis, unlike acute diffuse glomerulonephritis, rarely, if ever, cause disturbances in renal function and are therefore of little clinical significance<sup>6</sup>

In a condition which I have called benign hemorrhagic nephritis<sup>7</sup>, renal damage induced by remote foci of chronic infection such as diseased tonsils, results either in persistent or recurring hematuria The nature of the lesion is unknown because the patients do not die of their renal disease The bilateral hematuria is probably due to repeated rupture of damaged glomerular capillaries Although the hematuria may persist for months, the circulation through the glomerular capillaries remains unimpaired, for the condition never gives rise to hypertension, edema or to disturbances in renal function

*A Disease of the Body as a Whole*—Clinically as well as pathologically, acute glomerulonephritis is part of a diffuse systemic disturbance which affects the capillaries and finer ramifications of the vascular apparatus of the entire body Acute Bright's disease can be suspected clinically if albumin, casts and red blood cells appear suddenly in a previously normal urine during recovery from a streptococcus infection An early diagnosis can only be made positively, if in addition to the urinary findings there are clinical evidences of extrarenal vascular damage such as arterial hypertension, transient edema of the eyelids, face or body or clinical evidences of vascular disturbances in the skin, the brain, the ocular fundus or the myocardium

Disturbances of the myocardium may occur with the very onset of the disease and are common during the first weeks There is often tachycardia, arrhythmias, precordial discomfort The electrocardiogram is apt to show varying transient abnormalities from day to day, including T



Fig 2 A, B, C, D

A Subacute diffuse glomerulonephritis in a bacteria-free case of subacute bacterial endocarditis. Blood cultures were negative and no bacterial colonies were to be found in the vegetations. All glomeruli were in the same stage of the process. Death was due to renal insufficiency.

B Arterial lesion in the myocardium in patient dying of acute diffuse glomerulonephritis. Necrosis of a portion of the wall

occlusion of part of the lumen with platelet thrombus undergoing organization.

C Arterial lesions in the liver in acute diffuse glomerulonephritis. Necrosis of the wall of some arterioles and small arteries with complete occlusion of the lumen.

D Complete necrosis of the wall of a blood vessel in the adrenal in a case of acute diffuse glomerulonephritis.



wave inversions indicative of serious myocardial damage (Master<sup>8</sup>) (Fig 2 B) If the myocardial damage is severe, intense dyspnea and cyanosis may dominate the clinical picture of the first few weeks The venous pressure rises and there are physical signs of acute passive congestion in the lungs and liver At times congestive heart failure may end in death within the first week or two after the onset, before the renal damage has resulted in a significant degree of azotemia

Cardiac disturbances of this severity are due to vascular injuries affecting capillaries and arterioles of the myocardium There is often interstitial edema, but morphological changes in the endothelium of the interstitial capillaries may be difficult to demonstrate If the cardiac damage has been sufficiently severe, lesions of small branches of the coronary arteries can be found microscopically (Fig 2 B) These lesions may consist of necrosis of arterial walls, infiltrations of the media and adventitia with inflammatory cells, proliferative and desquamative lesions of the intima and obliteration of the lumen by thrombi (Fig 2 B) The vessel lesions are probably the result of acute damage and occlusion of capillaries and vasa-vasorum in the walls of the affected arteries

Similar arterial lesions may be found in the liver, the brain or in any of the viscera (Fig 2 C and D) Cerebral disturbances which sometimes characterize the first weeks of the disease may be due, at least in part, to such vascular injury Patients who recover from a severe attack of acute glomerulonephritis may suffer in after years from the late results of the extrarenal vascular lesions

*The Significance of the Renal Damage*—In many patients who succumb to acute glomerulonephritis it is often difficult to demonstrate morphologic changes in the walls of capillaries of other organs than the kidney although clinical evidences of disturbances in capillary function previously existed In the kidney, the peculiar arrangement of the capillaries of the glomeruli predisposes this organ to more profound and permanent damage Swelling of the endothelium of the glomerular capillaries is much more important anatomically and functionally than is swelling of capillary endothelium in other organs and tissues of the body The Bowman's capsule which envelops each glomerulus can stretch very little For this reason swelling and proliferation of glomerular endothelial cells results in complete obliteration of the capillary lumen, so that the glomeruli become bloodless Glomerular function and therefore renal function is promptly disturbed, for the glomeruli are the essential excre-

tory units. The bloodless condition of glomerular tufts soon results in necrosis of portions of various glomeruli and this destruction is apt to be permanent.

Since Reichel<sup>9</sup> and Loehlein<sup>10</sup>, pathologists, have emphasized the significant fact that every glomerulus is more or less involved, some severely or perhaps totally destroyed, others less severely affected so that some measure of anatomical and physiological recovery is possible. The term acute diffuse glomerulonephritis was chosen in order that the generalized nature of the process should not be forgotten.

Almost the entire circulation of the kidney must pass through the glomeruli before it enters a secondary system of capillaries which nourishes the delicate tubules (Peter<sup>11</sup>). The inability of much of the blood to pass the obstructions in the glomeruli results in damage to the tubules. Although the tubules have a great capacity to regenerate (Thorel<sup>12</sup>), they cannot do this very successfully as long as they receive an inadequate blood supply. Therefore cellular destruction of the regenerating tubules continues for some time, even for many months, while the circulation through the glomerular tufts slowly becomes re-established.

This results in the daily loss of great quantities of albumin, casts and cellular detritus. Patients who have survived the acute attack may subsequently develop marked hypoproteinemia and general anasarca due to the prolonged loss of albumin (Epstein<sup>13</sup>).

Twenty-five years ago there was much discussion concerning a rarer disease of the kidney, a pure tubular damage, for which Friedrich Muller<sup>14</sup> had advocated the term nephrosis. In this condition, prolonged loss of albumin in the urine also results in hypoproteinemia and anasarca. The clinical picture is therefore identical with that of the subacute stage of Bright's disease except that there is no history of an acute onset following scarlet fever or other streptococcus infection, no hypertension or history of hypertension at the onset and no red blood cells in the urine. Unfortunately, any or all of these characteristic symptoms may be absent in the waterlogged stage of subacute glomerulonephritis and the differential diagnosis from nephrosis is then difficult.

Popular interest in this rare disease was responsible twenty years ago for the fact that it became confused in the minds of physicians with that common clinical syndrome which had been described so well by Bright in 1827. Under the influence of Volhard<sup>15</sup> the well known clinical picture of the waterlogged patient with subacute Bright's disease has been re-

named, quite unnecessarily, the nephrotic stage of glomerulonephritis. The term is merely a synonym for Delafield's chronic parenchymatous nephritis, which is the parenchymatous stage of chronic glomerulonephritis.

*The Final Hypertensive Stage*—Patients who have had glomerulonephritis have suffered a severe and permanent damage to the kidney. Even though recovery may seem to have been complete so that for years no albumin or only a trace persists in the urine, the kidney remains susceptible to toxic damage. Pregnancy or an intercurrent infectious disease may precipitate a recurrence of marked albuminuria, edema and hypertension. Often arterial hypertension develops insidiously. Later there may appear a tendency to fixation of specific gravity or a reduction in urea clearance as evidence of progressive contraction of the kidneys. Ultimately, the nitrogenous constituents of the blood may begin to mount until the patient finally succumbs to the increasing azotemia.

The terminal picture of chronic Bright's disease is clinically indistinguishable from the terminal picture of primary hypertensive renal disease. In both, a long standing hypertension terminates in azotemia (dry uremia) due to progressive renal insufficiency. This clinical similarity in the termination of two diseases, so dissimilar in primary etiology and in their early stages, has been, and still is, a source of much confusion. The explanation is to be found in a study of the progressive changes in the arterial supply of the kidneys in both conditions and its influence in slowly reducing the remaining renal parenchyma (Baehr and Ritter<sup>16</sup>).

In both diseases progressive vascular changes are characteristic of the later stage (Fig 3). Numerous arterioles become thickened and sclerosed and the lumen of many of them becomes progressively narrower until completely occluded. The resulting ischemia affects many small areas of renal parenchyma so that they gradually become atrophic and sclerosed. Between these many sclerotic contracting areas, alternate areas of still functioning renal tissue carry on urinary excretion until the disease has finally progressed so far that insufficient functioning tissue remains.

In primary hypertensive renal disease, the fine vascular occlusions are scattered uniformly throughout the kidney, so that it gradually becomes contracted into a finely granular organ. In this primary contracted kidney of essential hypertension, the vascular disease develops in a previously normal organ. In the secondary contracted kidney of chronic Bright's

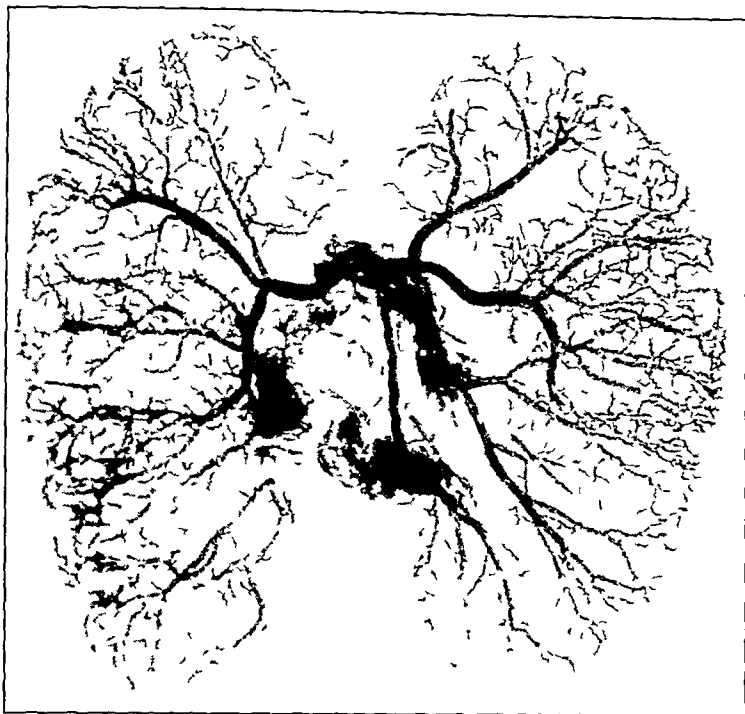


Fig 3—The kidney in chronic diffuse glomerulonephritis. Arterial tree injected with a barium gelatin mixture and then x-rayed. Note the marked reduction in vascularity due to progressive closure of arterioles and small arteries throughout the organ. The resulting progressive ischemic sclerosis of the renal parenchyma in chronic diffuse glomerulonephritis is identical in its effect with that of primary vascular disease of the kidney, the arteriolar nephrosclerosis of essential hypertension.

disease, the areas of functioning parenchyma between the numerous islands of ischemic sclerosis are already diseased and therefore function imperfectly. Renal insufficiency and death in uremia will therefore occur in chronic Bright's disease long before a degree of renal contraction has been reached which is comparable to that of the primary contracted kidney. For this reason, the secondary contracted kidney at autopsy is a somewhat larger organ than the primary contracted kidney. In both, however, the cause of the contraction is identical, the slowly progressive reduction in functioning renal parenchyma due to the vascular disease. There are some cases of chronic glomerulonephritis in which the atrophy is the result chiefly of the inflammation and secondary

cicatrization without significant vascular alterations

*Pathogenesis*—Glomerular lesions resembling human glomerulonephritis were produced experimentally in 1913 by Baehr<sup>17</sup> and by Christian and O'Hare<sup>18</sup> by the intravenous injection of uranium nitrate. These lesions were the direct result of the injected toxin upon the endothelium of the glomerular capillaries. The experiments threw no light upon the mechanism of Bright's disease for the following reasons:

Acute diffuse glomerulonephritis is almost invariably a sequel of some streptococcus infection such as scarlet fever, but it does not occur during the active period of the disease when the organisms or their bacterial toxins are reaching the kidneys in greatest concentration. Escherich and Schick<sup>19</sup> emphasized in 1912 that glomerulonephritis most commonly occurs during the second week after recovery. This important observation has received renewed emphasis during recent years as a result of the work of Lyttle<sup>20</sup>. By means of Addis counts on the urine of scarlet fever patients, he demonstrated that most of them show a sudden explosive outpouring of albumin, casts or red blood cells some time during the second week of convalescence, most commonly between the nineteenth and twenty-second day after the onset of the disease.

To explain this time relationship, Escherich and Schick, and later Friedemann and Deicher<sup>21</sup>, advanced the hypothesis that glomerulonephritis is an allergic reaction to the infecting organism. Recently, Longcope<sup>22</sup> demonstrated the presence of a high titer of streptolysins in the blood of patients suffering from postscarlatinal nephritis. However, a high titer of streptolysins is also frequently found in patients with rheumatic fever, a disease which is no longer thought to be due to allergy to the streptococcus. The hypothesis that glomerulonephritis is a local tissue reaction to a stage of bacterial allergy is still theoretical and as yet devoid of conclusive experimental support.

The nearest approach to experimental evidence is the recent work of Lukens and Longcope<sup>23</sup>. They have been able to reproduce glomerular lesions which resembled glomerulonephritis by the intra-arterial injection of streptococcus vaccine into rabbits which had previously been "sensitized" by intradermal injections of living streptococci. The presence of skin reaction to filtrates of hemolytic streptococci provided some evidence in Longcope's interesting experiments that the previous intradermal injections of living streptococci had actually "sensitized" his rabbits in the allergic sense. However, the pathological process involved

in glomerulonephritis is not a recognized characteristic of the known states of bacterial allergy

The work of Masugi<sup>24</sup> supplies still another possibility for speculation concerning the pathogenesis of glomerulonephritis. By means of the intravenous injection of heteronephrotoxic serum into laboratory animals, Masugi and more recently Smadel and Farr<sup>25</sup> have experimentally reproduced glomerulonephritis and even the chronic stages of Bright's disease. An hypothesis might therefore be proposed that products of cellular destruction caused by damage to the renal parenchyma during scarlet fever might act antigenically during convalescence and give rise to specific nephrotoxic substances. Such a theory is hardly plausible for destruction of renal parenchyma by diseases other than streptococcal infections does not give rise to glomerulonephritis. Moreover, streptococcal infections themselves, no matter how prolonged, do not cause glomerulonephritis unless the streptococci are killed off *and* the patient recovers from the infection.

This is best illustrated by our observations on streptococcemia and streptococcus endocarditis<sup>26</sup>. Among fifty-three consecutive patients with *Streptococcus hemolyticus* bacteriemia which came to autopsy, no instance of acute diffuse glomerulonephritis was found. Among ninety patients with subacute bacterial endocarditis in which the *Streptococcus viridans* was constantly demonstrable in the blood for months throughout the course of the disease, only one instance of acute glomerulonephritis was found postmortem.

In striking contrast to the negative findings in 143 cases of persistent streptococcemia is our experience with patients who recovered from a streptococcus infection. Among fifty-seven patients with subacute bacterial endocarditis who had killed off their bacteria and who died subsequently in the bacteria-free stage of the disease, diffuse glomerulonephritis occurred and was responsible for a uremic death in nineteen patients, an incidence of 33.3 per cent (Fig. 2 A). One died of acute glomerulonephritis, the other eighteen succumbed in the subacute or chronic stage of typical glomerulonephritis.

From these experiences, we can conclude that acute Bright's disease cannot be due to the direct damaging effect of streptococci or their toxins upon the kidney. Nor can it be caused by the mere killing off of streptococci, for this must be taking place constantly in patients with prolonged streptococcemias. It is evident that the sudden explosive occur-

rence of acute diffuse glomerulonephritis is a specific reaction, concerned in some still unknown manner with the mechanism of recovery from streptococcal infections

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## CLINICAL ASPECTS OF NEPHRITIS\*

ROBERT F. LOEB

Professor of Medicine College of Physicians and Surgeons

THE TERM nephritis embraces a number of morbid states with widely diversified etiological, pathological and clinical characteristics. An attempt to discuss the clinical aspects of various types of Bright's disease this evening would be futile. Likewise, a discussion of the symptomatology of one or more forms of nephritis could serve no constructive purpose. Consequently, I have elected to limit myself to the consideration of certain problems concerning that entity commonly known as glomerulonephritis.

All recent studies indicate that there is, as a rule, a close relationship between infection of the upper respiratory tract and the onset of acute glomerulonephritis. In recent and carefully controlled studies in which bacteriological and immunological observations have been made, the onset of acute glomerulonephritis has, in the vast majority of instances, been found to be associated with evidence of infection by the hemolytic streptococcus (Group A of Lancefield). Thus, Seegal and his coworkers found that the antistreptolysin titer of the blood was significantly increased in seventy-six of eighty consecutive patients suffering from acute glomerulonephritis, and in most of the cases it reached amazingly high levels. Longcope reported the presence of infection with the hemolytic streptococcus in 95 per cent of his patients.

In other instances, it now seems certain that acute glomerulonephritis develops secondary to infections due to agents other than the hemolytic streptococcus. A number of cases of acute nephritis have been reported following pneumococcal pneumonia. In most of these, secondary streptococcal infection has not been eliminated as a possible cause, but Seegal has recently followed two cases of postpneumonic nephritis in which there was no evidence of secondary streptococcal infection as determined by repeated antistreptolysin measurements. In bacterial endocarditis due

\* From the Department of Medicine, College of Physicians and Surgeons, Columbia University and the Presbyterian Hospital. Delivered November 3, 1937, in the Tenth Annual Graduate Fortnight.



to the streptococcus viridans also, glomerulonephritis not infrequently develops and is superimposed upon embolic nephritis without bacteriological or immunological evidence of invasion by the hemolytic streptococcus. It seems probable that in rare instances, acute glomerulonephritis may be initiated by still other organisms and that these need not necessarily gain entry to the body through the respiratory tract.

The role of infection in the etiology of *chronic* glomerulonephritis is far less clear than in the acute form of the disease, although exacerbations of chronic nephritis accompany or follow intercurrent infection with the streptococcus hemolyticus with striking regularity. In contrast with acute glomerulonephritis which usually develops ten to twenty days following an acute infection, chronic nephritis usually develops so insidiously that its onset is, as a rule, unrecognized. It seems certain that many cases of chronic nephritis begin as acute glomerular nephritis but the actual per cent is difficult to determine as it is often impossible to differentiate between the onset of acute nephritis and the exacerbation of an apparently quiescent chronic process. In Longcope's series about 40 per cent of the patients with acute nephritis developed active and progressive chronic nephritis. On the other hand, Lyttle, in studying children, in whom the outlook is admittedly favorable, has found that less than 5 per cent develop the chronic form of the disease.

In addition to the fact that chronic nephritis usually develops without definite relation to a preceding acute infection, there are also immunological differences between this and the acute form of the disease. Whereas the antistreptolysin titer of the blood may increase in chronic nephritis associated with streptococcal infection it rarely reaches the high levels seen in acute nephritis. The significance of this difference in the immune response in the acute and chronic forms of the disease remains to be determined.

*Mechanism of Glomerulonephritis*—While the relationship of hemolytic streptococcal infection to the onset of nephritis, at least in the acute form, is recognized, this knowledge has not as yet materially advanced our understanding of the mechanisms involved in the genesis of the disease. The fact that the onset of acute nephritis does not accompany but rather follows an acute infection offers evidence against the idea that the disease results from direct and immediate damage of the kidneys by bacteria or bacterial products. In 1912, Escherich and Schick expounded the idea that acute nephritis was not caused by acute infection but by

the immune reactions resulting from it. This concept may offer a satisfactory explanation for the latent period which elapses between the onset of infection and the onset of nephritis.

There have been many futile attempts to produce a disease in animals which shares the characteristics of glomerulonephritis in man. However, one line of approach, begun in 1900 by Lindemann and by Pierce in 1904 and elaborated by Masugi in 1929 and by Smadel and Farr since that time, has yielded interesting and important results. The general technique employed by these investigators is based upon the principle of the development of organ-specific antisera. If an emulsion of normal rat kidney is repeatedly injected into the peritoneum of a rabbit, a rabbit anti-rat kidney serum is produced. If one, two or three doses of this serum are injected intravenously into rats, acute nephritis develops. This disease may heal completely or it may go on to a chronic form associated with persistent and progressive albuminuria, cylindruria, edema, hypertension, anemia, nitrogen retention and a fatal decrease in renal function. The renal lesions bear a close resemblance to chronic glomerulonephritis in man.

The most significant feature of these studies is that they demonstrate the possibility of initiating chronic and progressive renal disease through the action of a single insult, in this case a dose of antikidney serum injected into a normal animal. Of added interest is the recent and important observation of Farr and Smadel that the course of the nephritis induced by the injection of nephrotoxic serum can be influenced by the amount of protein in the diet. If the diet of the rats contains only 5 per cent protein, the acute nephritis heals with great regularity in about three weeks. If, on the other hand, the diet contains 40 per cent protein, the disease progresses and the animals all die of chronic nephritis.

It is tempting to infer that a mechanism similar to that described in rats is responsible for glomerulonephritis in man. In order to extend the analogy, we must hypothecate that the hemolytic streptococcus or other bacteria produce somewhere in susceptible human beings nephrotoxic sera. These may give rise to acute nephritis which may or may not become chronic. It is possible that in man, as in the rat, another factor such as that of protein ingestion may serve to make progressive the disease initiated by a nephrotoxic serum. There is unfortunately, at the present time, no experimental evidence suggesting that nephrotoxic sera can be developed in response to the injection of bacterial products.

This speculative discussion has no practical application, but it indicates the trend of present day thought in relation to the possible mechanism involved in the production of glomerulonephritis. However, the observations on the deleterious effect of large amounts of protein in the diet are sufficiently striking to reopen the question of the place of protein in the diet in human nephritis.

The *diagnosis* of acute glomerulonephritis in its characteristic form offers but little difficulty. When, however, albumin, casts and red blood cells appear in the urine in small but definite quantities without extrarenal signs, either during or after an acute infection, the problem of diagnosis becomes difficult or even impossible. A number of students of nephritis circumvent these diagnostic dilemmas by applying the term focal nephritis to these doubtful cases, but in the writer's opinion the introduction of another term does not clarify the issue. If mild albuminuria, cylindruria and microscopic hematuria persist for more than one or two weeks, it seems probable that acute glomerulonephritis is present. If the changes disappear in a shorter time, it is best to admit that the diagnosis is uncertain. Minute decreases in renal function as measured by the urea clearance test may result from disorders other than nephritis and do not alone simplify the diagnostic problem. Frequently, often repeated urine examinations, a careful record of body weight which, in the absence of visible edema, may give evidence of water retention or diuresis and numerous blood pressure determinations may give transient but convincing evidence favoring the diagnosis of acute glomerulonephritis.

The difficulties besetting the physician in establishing a diagnosis of acute glomerulonephritis are emphasized by recent studies of urinary changes in acute rheumatic fever and in scarlet fever. In the former, in at least 15 per cent of the patients with the active form of the disease, red blood cells and small amounts of albumin appear in the urine at some time and yet only about 3 per cent prove to have associated acute glomerulonephritis at death. In scarlet fever, Lyttle, applying Addis' quantitative method for the determination of protein, casts and cells in the urine, found consistently a moderate transient increase above the accepted limits of normal. This occurred between eight and forty-five days after the onset of the attack of scarlet fever. Lyttle found similar changes in the urine after other infections due to the streptococcus hemolyticus, but did not find them with any regularity after infection with

other organisms. It seems unlikely that all patients suffering from scarlet fever and other streptococcal infections develop acute glomerulonephritis. Whether or not, however, the difference between this micro-nephritis or "renal irritation" and true acute glomerulonephritis is qualitative or quantitative cannot be settled at this time.

*The differentiation between acute glomerulonephritis and the chronic form of the disease* is of great importance because of the difference in prognosis and therapeutic indications. If urine examinations happen to have been made just prior to the onset of the attack, the problem is of course simple. Without knowledge of the medical background of the patient, it is often difficult and occasionally impossible to tell whether the patient's disease represents the beginning of acute nephritis or an acute exacerbation of chronic glomerulonephritis. If the latent period between acute infection and the appearance of renal disease is greater than ten days, it favors the diagnosis of acute nephritis because, in the chronic form of the disease, the flare-up usually occurs during the acute infection or shortly thereafter. When the signs of advanced and protracted renal disease are present, the diagnosis of chronic nephritis is justifiable. In the absence of these guides, diagnosis frequently has to be deferred until the subsequent course has been observed.

Patients with acute glomerulonephritis either recover completely or their disease progresses to the chronic form or they die during the acute attack. A fatal outcome occurs in less than 5 per cent of the cases. In children, complete recovery occurs in about 90 per cent of hospitalized patients but in adults the prognosis is definitely less favorable. However, it is difficult to determine the actual incidence of recovery because, as has been stated, an apparent acute nephritis may in reality represent an exacerbation of the chronic form of the disease, hitherto unrecognized. Furthermore, many patients with mild acute nephritis undoubtedly recover without ever coming to the attention of a physician and are consequently not included in statistical studies. Finally, in a number of mild cases, it is impossible to be certain that nephritis is present. Be that as it may, estimates of the frequency of recovery in adults vary from about 15 to 70 per cent.

It is impossible to predict the outcome of acute glomerulonephritis early in its course. However, in those instances in which the constitutional symptoms of the preceding infection have been severe, it appears to be particularly good. Furthermore, complete recovery occurs rapidly

in many patients even though they present alarming extrarenal manifestations early in the course of the disease, whereas chronic nephritis develops in others with an apparently benign form of the disease. When significant impairment of renal function persists for more than 3 or 4 months, the outlook for complete recovery is almost invariably bad.

The duration of the attack of acute glomerulonephritis varies enormously. In a number of cases, even when the diagnosis appears established beyond doubt, complete recovery may occur in the course of a few days. In other cases the disease may persist for more than a year and still terminate favorably. In these cases the extrarenal manifestations of edema, hypertension and nitrogen retention disappear, as a rule, in the course of a few weeks and the persistence of the disease process is demonstrable by the urinary changes alone.

According to Longcope and others, the duration of an attack of acute nephritis and the tendency to chronicity are definitely related to the persistence of infection by the hemolytic streptococcus. However, Seegal and his coworkers find that in a number of patients, the disease progresses in the absence of persistent or recurrent bacteriological or immunological evidence of infection. Furthermore, they have found that recovery may occur despite the persistence of definite infection.

Of great academic interest and also of great importance for the peace of mind of the patient is the fact that once completely recovered, i.e., after the disappearance of albumin, red cells and casts from the urine, there appears to be no danger of the development of chronic nephritis. Thus, E. N. Loeb, Seegal, Lyttle and Jost have shown in a series of eight patients, that following recovery from acute glomerulonephritis a second infection caused no return of nephritis. In these patients, the infection preceding the onset of the attack of acute nephritis and the second infection occurring after complete recovery were proven bacteriologically and by means of antistreptolysin determinations to be due to the streptococcus hemolyticus. In three other patients, transient hematuria or albuminuria or both developed with the second infection, but none of the eleven patients developed chronic glomerulonephritis.

I should like now to discuss a few points in relation to the diagnosis of chronic glomerulonephritis. The diagnosis is, as a rule, easily established on the basis of the continued presence of albuminuria, cylindruria and varying degrees of hematuria either with or without the extrarenal manifestations of the disease. At times, however, it presents a trying

problem and the difficulties in distinguishing the acute and chronic forms of the disease have been mentioned. The differentiation between chronic glomerulonephritis and arteriolar nephrosclerosis is sometimes impossible but is of little importance except for academic reasons.

The differentiation between the nephrotic phase of chronic glomerulonephritis and true nephrosis also offers difficulties and is of importance because in the latter complete recovery takes place in about 50 per cent of the cases. Both conditions have in common, massive albuminuria, edema, decrease in the serum protein content with a tendency toward inversion of the albumin-globulin ratio, lipemia and often lowering of the basal metabolic rate. The diagnosis of chronic nephritis becomes probable if, in addition to these signs, there be enlargement of the heart, marked hypertension, changes in the eyegrounds, significant impairment of renal function or numerous red blood cells in the urinary sediment. The age of the patient also has significance since true nephrosis rarely occurs in adults. The difficulties encountered in the diagnosis are exemplified by the following case record. A boy of fourteen developed headaches and edema about two weeks after a head cold. On examination, he had massive edema, and a blood pressure level which reached 160/100. His urine showed the presence of large amounts of albumin, many casts and occasional red cells. His blood urea rose to 100 mg per 100 cc. This patient was believed to have chronic glomerulonephritis of the nephrotic type. He subsequently died from pneumococcus peritonitis and examination postmortem demonstrated the presence of pure lipoid or true nephrosis.

The differentiation between latent glomerulonephritis and orthostatic albuminuria presents difficulties in adolescents in whom no significant disturbance of renal function can be determined by the usual tests. The evidence favors an orthostatic process if the albuminuria disappears with bed rest but this is, however, not entirely conclusive, as the albuminuria in some cases of latent nephritis may diminish greatly with rest and increase with activity. If hypertension or other extrarenal manifestations are present, the problem of diagnosis is simple. In a number of cases, only prolonged observation with repeated urine examinations will serve to clarify the diagnosis.

It must be borne in mind that the picture of advanced renal insufficiency often results from kidney disease other than chronic nephritis. In those cases in which the history is in doubt, and in which pyuria plays

a prominent part, if bouts of fever have been present or if the clinical picture is in any way unusual, it is essential that x-ray examination and pyelography be employed

Finally, it should be recognized that albuminuria, casts and red blood cells appear in the urine in cardiac decompensation, in jaundice and in severe febrile disease. Thus, in cardiac insufficiency, in addition to the urinary changes described, the blood urea may reach 0.70 gm per l or more, the blood urea clearance may be diminished and the phthalein excretion often falls to 30 per cent or even less. Hence, it is often impossible to state whether chronic nephritis is or is not present and decision must be postponed in such patients until cardiac compensation is re-established. If eyeground changes, fixation of the specific gravity of the urine, and marked hypertension accompany cardiac failure, it is probable that nephritis is also present.

While the *prognosis* in patients with chronic glomerulonephritis is ultimately bad, the velocity with which the disease reaches its fatal termination is extremely variable. Except in the terminal stages, it is practically impossible to predict the probable life span of a patient on the basis of clinical observations and laboratory studies, made at any one time. Repeated observations and studies of renal function made over a period of months or years are of far greater value insofar as they may reveal an approximate curve of the velocity of progression of the disease. Despite the most careful supervision, however, prediction of the course of chronic glomerulonephritis is hazardous. For example, a patient may be observed during an acute exacerbation of the disease. After some months, activity may subside and the patient may lead a normal and useful existence for many years before uremia develops. Thus, in a patient seen at the Presbyterian Hospital with massive edema, hypertension, nitrogen retention, albuminuria and hematuria, the blood pressure now, twenty years later, is normal and only albuminuria and cylindruria without impairment of renal function persist. In other cases of apparently the same initial severity, the disease may progress to a fatal termination in a few months.

There are certain criteria, which although not infallible, have real prognostic value. When the disease is associated with rapidly progressing hypertension, when severe anemia develops abruptly, when in the course of a few months the power of concentration is lost and when activity of the disease as manifested by copious microscopic hematuria persists

over a period of three to four months, the duration of life is usually less than two years. Furthermore, if decompensated renal function appears and the blood urea rises progressively to levels of perhaps 1 gram per l the prognosis is equally grave. The presence of papilledema, combined with hemorrhages and patches of exudate in the eyegrounds also usually indicates that the duration of life will be less than two years. The same outlook may be anticipated when the urea clearance falls below 10 per cent of normal or when the phthalein excretion fails completely.

In order to temper the significance of these dogmatic statements, I should like to mention briefly the record of one patient who broke all the accepted rules. In this girl, after six years of active glomerulonephritis, the excretion of phthalein in two hours was nil, her blood urea was 90 mg per 100 cc and her creatinine was 6 mg per 100 cc. Despite this, the patient worked most of the time during the following six years and annual observations showed not only the persistence of markedly impaired renal function but further accumulation of urea in the blood. The patient finally died in uremia and the diagnosis was confirmed at autopsy. Cases of this kind occur with sufficient frequency to warrant extreme caution in offering a bad prognosis for the probable duration of life.

Before concluding, I should like to comment briefly on the *treatment* of chronic nephritis. It must be recognized that, in the treatment of chronic glomerulonephritis, we are dealing with the problem of therapy in a disease which is incurable at the present time. Hence, the physical comfort of the patient and, still more important, his peace of mind, deserve first consideration. If this principle be kept in mind, the patient may be spared the distress and discomfort associated with measures such as unnecessary dietary restriction, excessive purging, sweating and colonic therapy which are not only futile but which may be actually harmful. This apparent therapeutic nihilism, I believe, in reality better serves to make the patient's existence tolerable than does over-energetic treatment. This point of view does not imply that a purely *laissez faire* attitude should be adopted. On the contrary, every effort should be made to introduce those measures which may retard the progress of the disease and it is essential that the patient be forewarned against those factors which appear to accelerate it.

In the *dietetic treatment* of chronic nephritis only questions of protein, salt and fluid deserve consideration. It is our impression that the



importance of *protein* restriction in some cases and of forced protein feeding in others has been over-emphasized in recent years. In chronic nephritis, characterized by albuminuria, cylindruria and some hematuria without edema or advanced renal insufficiency, there appears to be no reason for regulating the amount of protein in the diet beyond suggesting that the patient follow the adage of "moderation in all things." In the presence of nitrogen retention, the amount of protein should be restricted because large amounts undoubtedly contribute to the retention of nitrogenous products. In these patients, the amount of protein may perhaps ideally be reduced to 40 or 50 grams a day. If, however, anorexia results in loss of weight and strength, it is far better to allow the patient to choose his foodstuffs without regard to theoretical consideration than to have him burn his own body protein and increase his non-protein nitrogen retention from that source.

When Epstein pointed out the importance of hypoproteinemia in the genesis of nephrotic edema twenty years ago, he logically introduced high protein feeding to compensate for protein lost in the urine. We all employ this diet today in the treatment of the edematous chronic nephritic, but I think it is fair to say that we are almost always disappointed in its effect upon the level of the serum proteins and amount of edema present. Nevertheless, it seems rational to attempt to maintain nitrogen balance in these patients in order to prevent the further depletion of serum albumin. This can usually be accomplished by the ingestion of about 100 to 120 grams of protein a day. I sincerely doubt that diets much higher in their protein content accomplish more and, in addition, they are distasteful to the patient deprived of salt.

Our feeling concerning the place of salt restriction can be expressed in a few words. Sodium salts are essential for the formation of edema fluid. Hence, in the presence of abnormal fluid retention, regardless of the reason for its appearance, rigid limitation of sodium must be enforced. It is our opinion that there is no other sound basis for salt restriction in the treatment of nephritis and that employment of this therapeutic measure in the absence of edema often accentuates anorexia, nausea and vomiting.

In patients with chronic nephritis, consideration of *fluid* ingestion is important only under two conditions. First, in the presence of edema, the intake of water should be restricted in accordance with the degree of retention, the acuteness of the symptoms and the presence of cardiac

insufficiency. Second, with the advance of renal insufficiency, the fluid intake should be increased to compensate for the loss of the power of concentration. If, however, the intake of fluid exceeds that amount which can be eliminated by the renal units still capable of function, edema will appear.

The use of diuretics is contraindicated in patients with chronic nephritis exhibiting either hematuria, gross or microscopic, or significant impairment of renal function.

The importance of the close relationship between recurrent or persistent infection of the upper respiratory tract and exacerbations of chronic nephritis can not be over-emphasized. Both the physician and the patient must look upon even a mild cold as a matter of concern and should treat the disorder accordingly. Tonsillectomy, in my opinion, should be performed routinely in patients with early nephritis and sinusitis merits rigorous attack. When, however, glomerulonephritis has progressed to the stage of advanced renal insufficiency, operative treatment of disease of the nose and throat has no place.

In conclusion, I should like to say that this brief sketch of certain aspects of glomerulonephritis in no way does justice to the scope of the title and I must add that I have considered only a few phases of the disease which seem to have particular interest at the present time.

## CALCULOUS DISEASE IN THE URINARY TRACT\*

*The Formation of Stone*

LINWOOD D KEYSER

Surgeon, Roanoke General Hospital, Roanoke, Virginia

THE PROCESS of stone formation in the urinary tract has been one of the most elusive of medical problems. Prior to 1917, when Osborne, Mendel and Ferry made the chance observation that rats fed on a diet deficient in vitamin A developed urinary calculi, little purposive effort at solving the problem had been made. Through the ages, it is true, that man speculated with vagaries of the imagination concerning water, the soil, uric acid and lime excretion as etiologic factors. Latterly with the development of the modern concept of bacterial infection, of urostitis, and of metabolic disorder, hypothetical consideration of the influence of these agencies has been championed by many clinicians. Since 1920 a series of experimenters and clinicians have diligently approached the problem in the laboratory and at the bedside. While the chemists and bacteriologists have been of help, it is interesting to note that many of our best contributions have come from the urologist himself who has at least investigated, stimulated, and actively helped his colleagues in the basic sciences.

What do we know of lithiasis today? It shall be my purpose to correlate the pertinent data which has aggregated in the last few years and to establish the thesis that stone may arise in several ways—that it is an end result of several types of colloidal crystalline aggregation into a solid mass. I shall attempt to show the grosser features of some of these processes and finally to point out how far we may attempt to control stone disease within the limits of our present scientific knowledge.

THE COLLOID—CRYSTALLOID PRECIPITATION MECHANISM  
CRYSTALLINE HYPEREXCRETION AS A CAUSE OF STONE

Stone arises when colloids and crystalline matter are simultaneously precipitated in the free urinary stream. The colloidal gel enmeshes

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agglutinated or fusing crystals and forms the organic framework around and within which these crystals are laid down as building elements. The process may be stimulated, first by the hyperexcretion of excessive crystalline material through the kidneys beyond the power of the urine with a given pH, colloid and salt content to maintain solubility, second, by the entrance of foreign colloid into the urinary stream. Hypothetically we must consider further the possibility of stone formation by the precipitation of normal colloid from the state of a sol to that of a gel by factors which are as yet unknown.

The scientific establishment of the colloid-crystalloid precipitation mechanism rests on the following facts:

1. Crystalloids, e.g. calcium oxalate, precipitated from colloidal solutions *in vitro* change from isolated noncoalescent crystals to those of fusing stone-forming type (Raney, Ord, Shattock) (Fig. 1)

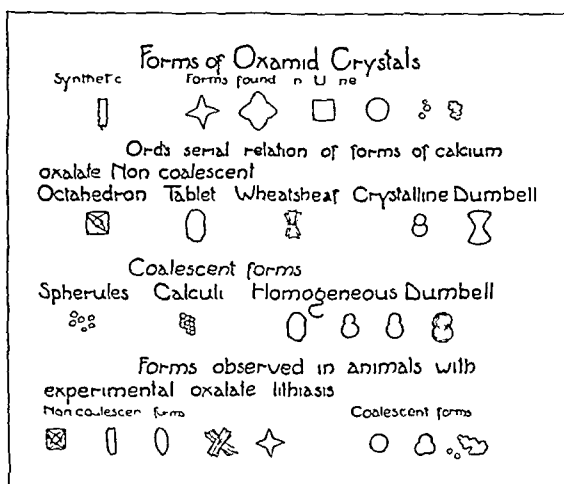


Fig. 1

A diagrammatic sketch of the serial relationship of noncoalescent and coalescent forms of oxamide and of calcium oxalate crystals. W. M. Ord in 1871 recognized the power of colloids *in vitro* to modify the morphology of crystalline matter and traced the relationship of noncoalescent and coalescent varieties of calcium oxalate as shown above. Later he showed with Shattock that the coalescent forms constituted the structural units of calculi as seen microscopically.

2. Hyperexcretion of oxamide, of calcium oxalate and more recently of calcium carbonate, experimentally produced in animals, is associated with agglutination of crystals in an organic framework of colloid to form calculi. This process takes place in the urinary stream, is not confined to the papillae and does not seem to be related



Fig 2

Bilateral lithiasis in a rabbit fed oxamide daily for seventeen days, larger masses lie behind the free margin where the calices are attached to the renal parenchyma

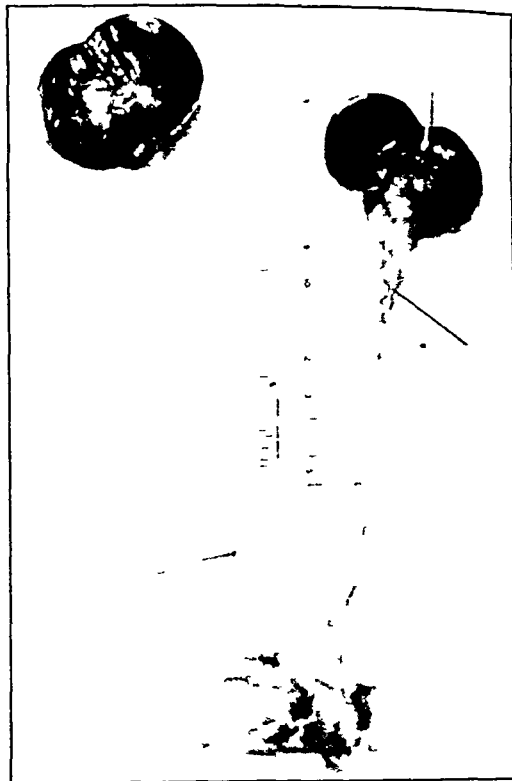


Fig 4

Calcium carbonate stones in kidneys and ureters of rabbit. Result of feeding 1 gm calcium carbonate to 2 kg rabbit daily over 4 months



Fig 3

Calcium oxalate stones in bladder. Result of intense oxaluria produced by injection of normal butyl oxalate and calcium chloride



Fig 5

Oxamide crystals as observed in urine under the influence of the urinary colloids. These crystals have assumed a morphology altogether different from the synthetic form. We can trace the evolution of crystals through noncoalescent crosses, crosses with interstitial spaces partly filled out, squared forms and coallescent spheroids.

- to lime salt impregnation of cells. However, casts of agglutinated crystals are noted at times in the collecting tubules (Figs 2, 3, 4)
- 3 Artificial concretions have been formed *in vitro* by precipitating fibrin and calcium phosphate simultaneously from the same solution (Schade)
  - 4 Oxamide fed to animals and excreted in the urine undergoes crystalline change to a stone forming type by adsorbing colloid. The process can be repeated in the test tube, where synthetic oxamide dissolved in urine on boiling and reprecipitated on cooling undergoes a change in morphology to spherular stone forming crystals (Figs 5, 6)

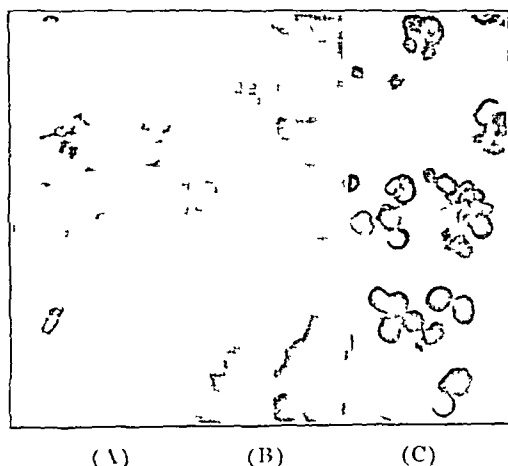


Fig 6

a—Crystals of pure oxamide synthetically prepared  
λ300

b—Deposit obtained when synthetic oxamide is dissolved in boiling urine and allowed to precipitate on cooling. The crystals are the developing cross type, they are pigmented and show marked tendency to fuse into small agglomerations. This sediment

is indistinguishable from that in the urine of rabbits fed on oxamide λ300

c—Oxamide crystals deposited *in vitro* from urine in which the synthetic chemical was dissolved by boiling, showing the perfect smooth sphere and no tendency to fusion λ200

- 5 Experimental hyperexcretion of calcium oxalate and carbonate associated with calculus formation shows a similar crystalline morphologic change (Fig 7). The clinical type of stone which agrees in detail with hyperexcretion calculus is that associated with hyperparathyroidism. High blood calcium and low phosphorus, a shift of excessive excretion of calcium from the alimentary to the urinary tract, the occurrence of calcium phosphate casts and amorphous spheroidal crystals in the urine, the tendency to bilateral lithiasis, and

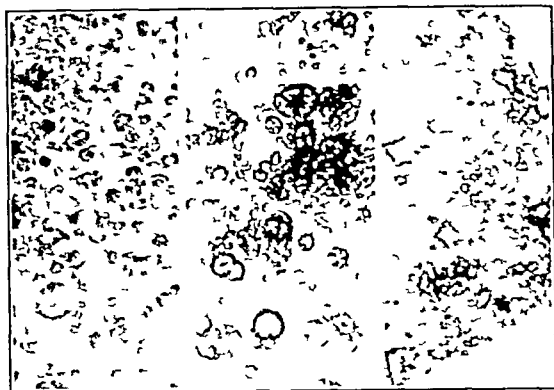


Fig 7

Small calcium oxalate calculi experimentally produced as in text crushed on slides to show crystalline elements in structures. Note that the small fusing spheroids constitute the structural units

finally, the cessation of the stone-forming process when the hyperparathyroidism is corrected with restoration of a normal calcium phosphorus excretion, establish the fact that hyperexcretion of calcium phosphate has been the cause of the stone formation

The incidence of calculus in association with phosphaturia, ovaluria and uraturia in excessive amounts has not been definitely determined. We do know that stone is frequent in these diseases, but clinical reports as to the quantitative urinary excretion of the salts involved are lacking. However, the impression remains that gouty individuals on excessive urate elimination frequently have ureteral colic. Indeed, in a few instances of recurrent urate calculi, we have found the blood uric acid elevated. It is therefore likely, but not established, let us emphasize, that excretion of phosphate, oxalate and urate may progress quantitatively to the point of crystalline precipitation at a given pH, colloid and salt concentration. These crystals are isolated units as a rule and pass with the urine. However, when the excretion exceeds a certain threshold level, crystalloid and colloid precipitation takes place simultaneously with concrement formation as a result.

- 6 Cystin and xanthin stones owe their origin to the entrance of foreign water insoluble crystalline matter into the urinary stream by reason of metabolic error. Hence the mechanism of their formation appears to correspond essentially to that of the hyperexcretion type

- 7 Fibrin calculi appear to be our only known example of stone resulting from a foreign colloid (fibrinogen) being precipitated simultaneously with lime salts. The clinical cases parallel in some measure Schade's test tube experiment, as in these stones fibrin and calcium salts are found precipitated together.

Again the probability exists, theoretically at least, that colloidal changes may take place in the urine with consequent loss of urinary solution power and precipitation of crystalline matter which is being excreted in amounts normally held in solution or deposited as isolated units. The existence and cause of such colloidal change has not been demonstrated to date, yet such a possibility cannot be excluded from consideration. This concept might explain why some phosphaturias, ovalurias and uraturias escape calculous formation and others do not.

#### THE CRYSTALLINE ENCRUSTATION IMPREGNATION MECHANISM SPECIFIC INFECTION AS A CAUSE OF STONE

Stones may arise from the impregnation or encrustation of cells, bacteria, tissues, or foreign bodies with urinary salts. This salt deposition may occur within or upon the cell, within certain layers of tissues, such as in subepithelial plaques (as described by Randall), upon clumps of bacteria or upon any foreign body. The deposition of lime salts in necrobiotic tissues has not been satisfactorily clarified nor will I enter at this time into the many theories which pathologists have advanced to explain the process. However, the scientific establishment of a salt encrustation impregnation mechanism in forming stone rests upon the following facts:

- 1 Stone may be produced in animals by infection with specific stone-forming bacteria isolated from the urinary tract of patients with rapidly growing or recurrent calculi. This has been demonstrated by Hegar and Magath with proteus, by myself with streptococci, and by Hellstrom and Hryntshak with staphylococci, while Rosenow and Meisser with streptococci from the teeth of such patients reproduced stone in dogs. Hegar and Magath found the bladder mucosa of rabbits to be impregnated with lime salts as the result of infection with the alkaline urea splitting proteus. I likewise noted calcium impregnation of urinary tract epithelium under such conditions after infection with streptococci and could trace



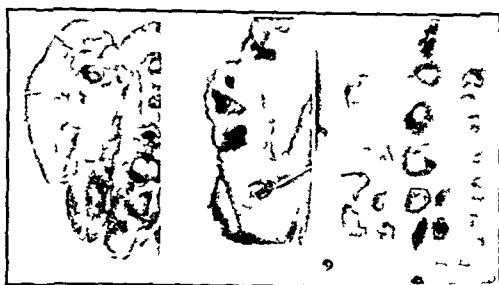
histogenetically the breaking off of particles of this lime-encrusted tissue to grow and form free vesical, ureteral and renal calculi (Figs 8, 9)

- 2 In a series of human kidneys with calculous pyonephrosis, sections of tissue adjacent to stones in calyces when stained with Von Kossa's silver nitrate method for calcium phosphate, show lime impregnated cells and I have been able to trace the histogenesis of stone from this calcified renal epithelium, portions of the calcified material breaking off to form free calculi, or at times remaining attached to the subjacent tissue, the mass growing into the calycal lumen. In histologic detail this process corresponds to that observed in experimental animals with infectious calculus (Fig 10)
- 3 Randall has shown that stone frequently arises from subepithelial salt deposition in papillary "milk plaques." This process he feels may not be associated with infection, but its actual cause is as yet indeterminate
- 4 Again stone can be produced experimentally in many species of animals by extreme dietary starvation in vitamin A and B, especially the former. The histogenetic study of such calculus reveals keratinization of urinary epithelium with an intensely alkaline crystalline urine, in consequence of which deposition of lime salts takes place within and upon this effete epithelium (Osborne, Mendel, Ferry, McCarrison, Fujimake, VanLeersum, Peacock, Higgins, Grossman). Infection appears late as a rule and after the lime salt deposition has begun. The role of infection in producing larger calculi is indeterminate. However, the fundamental picture of lime salt encrustation impregnation mechanism appears again
- 5 The association of calculi, chiefly the carbonate and phosphate variety, with alkaline urea splitting organisms such as the proteus, streptococci and staphylococci is well known. These are the secondary calculi of Albarran in contradistinction to the primary or assumedly aseptic calculi, composed of urates and crystalline phosphates and carbonate, which are more often found in neutral or
- 6 Acid urines. The reproduction of such secondary calculi by intra-urethral, dental canal and direct vesical infection by different workers reestablish specific bacteria from stone-forming patients, the failure to reproduce stone with non-specific bacteria, together with the demon-



Fig 8

Infectious calculosis produced by infection of rabbits with streptococci from the urine of a stone forming patient. Note encrusted cystitis, dilated ureters and pyonephrosis five weeks after infection.



(A)



(B)

Fig 10

Histogenesis of calyceal stone in human kidney removed at operation.

a—Areas surrounding calyceal stone removed for section and stained by Von Kossa method for calcium.

b—Above areas stained with Von Kossa stain. Lime salt deposition within and upon epithelium growing into lumen of calyx and breaking off to form free calculi.



(A)

(B)

(C)

Fig 9

Histogenesis of infectious lithiasis in rabbits bladder as shown in Fig 8.

a—Necrobiotic epithelium produced by chemical irritation.

b—Encrusted epithelium breaking off to form calculi.

c—Encrustation of surface cells beginning.

stration of cell impregnation with lime salts both in animal and human urinary tracts, demands that we accept specific bacterial infection as the cause of at least one variety of stone. These calculi are unilateral and affect one site more often than the bilateral stones or those occurring at several sites in the urinary tract which are found when the hyperexcretion mechanism is at fault. They frequently cease to form after removal when drainage and elimination of the infection are established.

- 6 The clinical occurrence of vitamin deficiency stone is as yet speculative. The geographic incidence of calculus, its relative disappearance in children of today as the result of better dietary, its infrequency in negroes, etc., are explained by the vitamin content of the diet. Photobiometric tests such as that of Jeans are being used to determine ophthalmologic dark adaptation as a measure of vitamin A deficiency. These tests initially seem to support vitamin A deficiency as a factor in stone formation in many instances. Yet the evidence is incomplete and not conclusive. I have discussed elsewhere why I cannot support the vitamin A theory with enthusiasm. Patients with stone for the most part eat a dietary reasonably adequate in vitamin A. Whether or not they absorb it properly and whether or not the relatively slight lack of this vitamin is associated with stone and no other deficiency symptoms, is very questionable.

### THE FACTOR OF URINARY REACTION

The solution of stone-forming material in urine is maintained by the protective urinary colloids, such as mucin, fibrinogen, chondroitin sulphuric acid, etc., by the quantity of soluble salts and other solids present and also by the temperature, the dilution and the reaction of the urine. Thus urea, a so-called hydrotrophic compound, increases the solubility of calcium oxalate. The relative role of colloids and organic solids in maintaining solubility has recently been challenged and as we have little tangible knowledge of their practical control, I shall not review this controversy. The H-ion concentration, however, is a great factor in maintaining solution and within certain limits determines the composition of the stone-forming material.

Amorphous phosphates, and carbonates and triple phosphates are precipitated in urines of intense alkalinity, whereas the urates, oxalates and crystalline phosphates and carbonates with occasional exceptions

are thrown down from urines of relative neutrality or acidity (oxalates average pH 5.9, urates pH 5.6, phosphates pH 6.2, uric acid pH 6.5) (Maslow)

Certain authors have held alkalinity itself as a cause of alkaline earth stones. The occurrence of such stones in patients on an alkaline ulcer dietary is cited. However, all ranges of pH are noted in normal individuals without stone and the factors of infection or of hyperexcretion would seem more likely causes of lithiasis in such cases. Certainly some factor other than alkalinity is necessary before stone will form.

Yet by changing the H-ion concentration of the urine the stone forming process may be definitely altered. In infectious alkaline experimental lithiasis, stone will not form if the animal is fed on an acid ash dietary such as oats, while a highly alkaline dietary seems to intensify the process.

#### THE FACTOR OF UROSTASIS

The clinical and experimental evidence for urostasis as a primary cause of stone is entirely lacking. In maintaining infection and stagnation, however, it is a matter of great moment. When the stone-forming process is active, when lime salts are being deposited by bacterial action on effete cells or when the colloid-crystalloid coagulation of hyperexcretion is present, it is easy to understand how urostasis augments the retention and growth of stony particles. The experimental evidence for this has been cited in other reports.

Hence in the preventive therapy against recurrence of stone, urostasis is perhaps our greatest point of attack. The removal of obstruction occupies a place equally important with the eradication of infections and the administration of diets and drugs.

#### OTHER FACTORS IN GENESIS OF CALCULI

Stones associated with fractures and infectious diseases of bones, with injuries to the vertebral column and spinal cord, come up for consideration. Our knowledge concerning their etiology is not exact and time does not permit an account of the theories that have been advanced to explain their incidence. In bone disease a disturbance of the calcium phosphorus excretion is held, not without controversy to be sure, to be the cause. The tendency to bilaterality of such stones, their apparent initial independence of infection, supports the theory of

hyperecretion as the mechanism at fault In "osteitis deformans", Goldstein and Abeshouse feel that vitamin A deficiency may explain the increased incidence of calculous disease In "osteitis fibrosa cystica" increased calcium excretion in association with hyperparathyroidism seems the cause, while in rickets the frequent incidence of lithiasis is explained again as due to an increased calcium phosphorus excretion

Bacterial clumps encrusted with urinary calculi, i e, the bacterial nuclei stones, such as have been described by Eisenstadt, Scholl and others, are interesting Hellstrom has shown staphylococci in layers within the laminations of alkaline calculi Whether the bacterial clump acts as a foreign body or as a urea splitting agent to precipitate lime salts on effete cells is controversial, although the weight of evidence supports the latter conclusion

The factors of renal trauma, formation of stones on sutures, in fistulous tracts, in association with tuberculosis and cancer offer material for speculation which for the time must be passed by, as exact evidence of their mechanism of formation is lacking

From this background, however, we must conclude that stone is not a disease entity Rather it is a physical manifestation of crystalline matter, i e, a change in form which results from several physico-chemical mechanisms Two of these mechanisms, viz, the colloid-crystalloid precipitation type as produced by crystalline hyperecretion and the encrustation-impregnation type produced by specific bacterial action have been established and demonstrated on experimental and clinical grounds Nevertheless, other mechanisms must yet be determined to explain the manifold aspects which stone disease may assume

#### DISSOLUTION OF URINARY CALCULI

Crowell's dissolution of cystin calculi by urinary alkalinization and Randall's use of phosphoric acid to dissolve small fragments marked the first steps in this line of therapy The solvent for stone has long been sought Being impressed with the alkalinity of the urine associated with certain alkaline earth stones, I attempted to shift the urinary reaction to the acid side using dilute nitro-hydrochloric acid, ammonium nitrite and chloride and an acid ash diet In 1933 I reported with x-ray demonstration partial dissolution of a carbonatic calculus by such urinary acidification, the first instance of its kind (Fig 11) Since then I have been successful in causing the disintegration and passage of six alkaline



Fig 11

Large carbonatic calculus pyonephrosis in right kidney treated by nephrectomy. Recurrence in left kidney after thirty days. Streptococcic infection. Reduction in size of calculous mass with two small fragments remaining after thirty days of urinary acidification and pelvic lavage with phosphoric acid.

calculi by urinary acidification, and of two uratic stones by intense urinary alkalinization.

The development of the acid-base diets with addition of vitamin A was popularized by the reports of Higgins and others, so that the method has enjoyed a fair period of trial in the hands of American urologists. Undoubtedly too much was expected of the method, as the results on the whole have been disappointing. The report of Oppenheimer and Pollack from Beer's Clinic is exemplary of the usual failures that have been obtained by this type of therapy when careful statistical tabulation of cases is carried out.

Recently-formed, soft concretions of calcium phosphate and carbonate do frequently disappear on urinary acidification. Dense, well-defined calculi of long standing do not respond. Small stones in calyces in well-draining and well-functioning kidneys remain unaffected for years, as do unimpacted ureteral stones, both of which one would believe to be amenable to such therapy.

In this connection the study of dissolution of surgically removed calculi in weak acids *in vitro* has been interesting. Most carbonatic and phosphatic stones become soft and disintegrated on their surface, but soon a harder resistant layer is encountered upon which the acid fails to act. We fail to remember the organic colloidal matrix in the stone structure, the latter being resistant to weak acid or alkali as it is composed of irreversible colloidal "gel" in which crystals have become enmeshed in the process of precipitation.

The principle of acid base shift of the urine is of necessity bound to fail even with good renal secretion and proper drainage. The following cases illustrate success and failure of this therapy.

E G B, male, aet, 42—Recurrent ureteral calculi of ammonium magnesium phosphate over ten year period. Recurrence stopped by ureteral dilatation and urinary acidification. One small calculus persists in left kidney over nine year period in spite of periods of prolonged urinary acidification and forced vitamin A administration (Fig 12)

L W, nurse, aet, 35—Persistent right ureteral colic. Urinary acidification and vitamin A over two month period. Finally passage of small non-opaque calcium carbonate calculus which easily dissolved in acid in test tube.

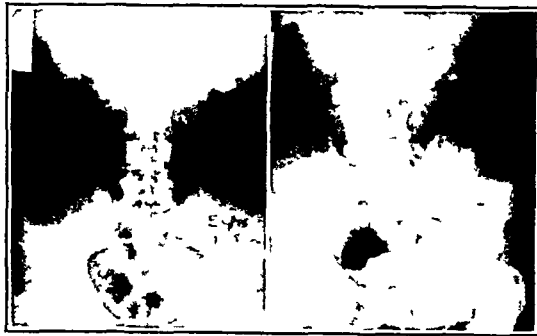


Fig 12

G T B, male, aet, 32—Recurrent phosphatic calculus at left uretero-pelvic juncture after two years. Partial dissolution of stone and passage after two weeks urinary acidification (Fig 13)

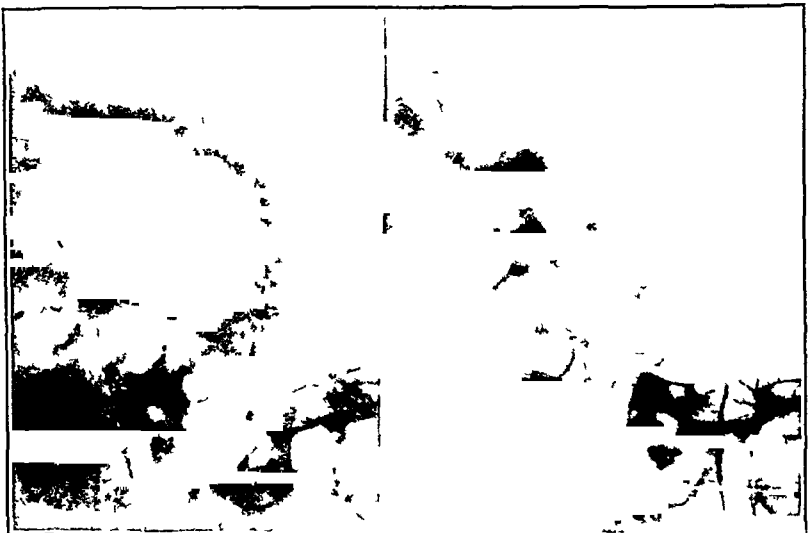


Fig 13

Mrs G I B (wife of G I B), female, æt, 30—Stone in right ureter Good kidney function Urine alkaline After four months vitamin A and acidification therapy *failure* to dissolve Removal by ureterolithotomy Phosphate calculus (Fig 14)



Fig 14

Mrs T O B, nurse, æt, 30—Recurrent calculus left upper calyx two years after removal of right kidney for calculous pyonephrosis Observed over a period of six years with frequent ureteral dilatation, vitamin A and acidification of previously alkaline urine Stone remained stationary in size Removal by pelvolithotomy (Fig 15)



Fig 15

The direction in which to shift the urinary reaction is not always easy of clinical application Certain uratic and oxalatic calculi, fibrin types and phosphatic varieties are found with acid and alkaline, with infected and uninfected urines No single dietary or drug therapy can be expected to give consistent results Each case must be studied individually Stones are almost always more or less mixed in chemical composition This varies with the previous diet, individual metabolic trends and consequent variation in the amount of crystalline stone-



Mrs O C B, female, aet, 50—Bilateral stag horn calculi. Calcium and phosphorus normal in blood. Alkaline urine with proteus infection. Could not acidify. Poor renal function. Death from hemorrhage after operative removal of left calculus. Calcium phosphate in type (Fig 16)



Fig 16



Fig 17

O C B, male, aet, 50, husband of Mrs O C B—First cousins. Bilateral calculous pyonephrosis. Calcium and phosphorus normal in blood. Alkaline urine with proteus infection. Infection reduced by sulfanilamide and urine acidified by diet and acid therapy pushed to point of tolerance. Vitamin A administered. Operation to date refused. No change in size of calculi. Course progressively downhill with increasing renal insufficiency (Fig 17)

forming material excreted. The urinary dilution, the quantity and kind of colloidal matter present, the H-ion concentration, factors constantly changing from hour to hour during the day, come into play. Only within narrow limits can we attempt to control them clinically. Given a patient with calculus we can only conjecture as to the possible relationship of these factors when the stone actually began to form. How to deal with laminated stones where urates, phosphates and oxalates preponderate in different layers, is from the standpoint of shifting the urinary reaction, an unanswerable problem. Hence the purposive dissolution of stone with the present methods is unlikely in an individual case and unless certain circumstances prohibit surgical or cystoscopic removal, dissolution should be attempted only for a short period and with softer types of stone. If no change in size is noticeable within a few weeks, further effort along this line will likely fail and prolonged maintenance of high acidity or alkalinity is not without hazard to the patient's urinary tract.

## PREVENTION OF RECURRENCE OF URINARY CALCULI

How far are we justified in applying our present knowledge to the important problem of recurrence of stone after surgical removal? I feel that by the application of certain principles which are consistent with our concepts of etiology much of practical value may be accomplished. A system of therapy which I have employed satisfactorily with certain modifications during the past seven years may be outlined as follows:

- 1 *Remove all stones and fragments as far as possible by surgery or cystoscopy*
- 2 *A qualitative chemical analysis of the stone removed should be carried out immediately*
- 3 *X-ray should be made immediately and at intervals of six months to one year for several years after operation*
- 4 *Seek and correct possibly related metabolic errors* The blood uric acid, serum calcium and blood phosphorus and phosphatase determinations should be routine observations. Cystinuria should be investigated. If hyperparathyroidism is suspected, x-rays of the bones and other pertinent data are to be obtained.
- 5 *The diet should be regulated with regard to the chemical composition of the stone* Dietary regulation assumes two aspects. First, the administration of a diet which will deplete exogenous supply of the stone-forming material, e.g. a low purin diet in uratic calculi, or a low oxalate dietary in oxalatic stone. Second, a dietary such as the acid or alkaline ash type which attempts to change the urinary reaction to the point of maximal urinary solution of the stone-forming chemical. Combinations of the two may be and should be attempted.

As for uratic calculi, the consistency with which these stones are associated with a hyperexcretion of uric acid is not known. However, intense urinary alkalinization is attendant upon disappearance of urate crystals from the urine. Therefore, a low purin alkaline ash diet is theoretically ideal here.

Oxalatic stone presents a problem. Exogenous sources should be excluded by low oxalate dietary. However, as Neville has pointed out, the source of oxaluria is probably endogenous, being associated with vitamin B-D deficiency. Oxaluria may be corrected by administration of these vitamins. While oxalates are precipitated in a wide range of urinary reaction, their solubility is perhaps better at a higher acid range.

Therefore, a high acid ash diet, low in oxalates, and rich in vitamin B and D is to be given

Phosphate and carbonate stones require a high acid dietary Control from the standpoint of exogenous sources seems impracticable Cystin is held in solution in alkaline urines Hence the basic diet is indicated

6 *Administer Vitamin A*—The controversial status of vitamin A in lithiasis has been mentioned Nevertheless the tonic effect of this vitamin on epithelial structures is indisputable and if tolerated by the already much dieted patient it should be given

7 *Eliminate urinary and focal infection* Gram stained smears and cultures of the urine from the bladder and each kidney should be made at the initial urologic examination

Oral antiseptic drugs may aid and the ketogenic diet or mandelic acid therapy may be tried with success Neoarsphenamine in coccal infections is of value However, coccal and proteus infections are most resistant and do not consistently respond to any treatment with which I am familiar Sulfanilamide cautiously used may reduce proteus infection in alkaline urine and after this infection is eliminated urinary acidification may be accomplished when it has previously not been obtainable

Focal infection should be routinely removed Dental, tonsillar, prostatic, cervical, and alimentary tract infections demand especial care

8 *Establish satisfactory renal and ureteral drainage* In the attack on urosthiasis I routinely practice periodic postoperative lavage with the free use of indwelling catheters and ureteral dilatation with bulbs In spite of sharp controversy concerning this procedure, I feel that it is one of our best therapeutic measures in treating any type of chronic non-tuberculous urinary infection Nephrostomy, suspension of the kidney, removal of vesical neck obstruction are to be carried out when indicated Lavage with phosphoric acid in 1 to 2 per cent solution may dissolve encrustation, sand, or minute calculi The dilated ureter may afford passage to small concretions Sacrifice the offending kidney only as a last resort

9 *Shift the urinary reaction to the range which will best keep the stone-forming crystals in solution* This feature has been previously dealt with At the outset it is important to determine the H-ion concentration several times daily The urine from each kidney should be separately studied with indwelling catheters The patient should be instructed to make his own H-ion determination either with a LaMotte or similar

indicator or with methyl red, nitrazene, or chlorphenol red paper. There is a potential danger in keeping the urine at an intensely acid or alkaline range over a long period of time. Systemic acidosis may be produced by too large or too long continued dosage of acid drugs and even nephritis can occur. For this reason, patients on such a regimen should be under constant observation by an understanding urologist who is familiar with this type of work. Chute has called attention to the fact that ammonium salts may actually form a source of food for urea splitting organisms if urinary acidity is not obtained and that urinary acidification will increase the elimination of calcium salts in the urine. Such calcium hyperexcretion may thus theoretically promote the growth of stone.

10. Patients with fractures, infections or other disease of bone, those with spinal cord lesions, renal trauma, or patients long bed-ridden should have their urine kept acid by diet and drugs and furnished ample vitamins as a prophylaxis against stone.

In 1933 I reported sixteen cases of rapidly recurrent calculi which had had their cycle of recurrence of from one to nine years permanently broken by the use of such measures. Since that time numerous similar cases have been treated successfully by myself and others.

The application of these principles is not easy, and requires an unusual degree of care as to detail on the part of the urologist and the utmost in cooperation on the part of the patient. Certain cases of rapidly recurrent calculi are baffling and at times impossible to correct. Yet we are reducing recurrence according to statistical information to a lower percentage level each year.

### CONCLUSION

Thus I have attempted to present to you the facts known regarding the etiology and prevention of urinary lithiasis. Admittedly the story is long and tangled. Nevertheless present day concepts give us a working basis, a point from which to start that was not existent twenty years ago. Scientific knowledge progresses by a process of evolution in which many investigators take part. With the intense interest at present being shown in this problem in many centers by earnest workers, I feel that it is not too much to prophesy that within a few years much will be added to give us a clearer understanding of this most interesting clinical phenomenon, stone in the urinary tract.

*With Comments on the Treatment of Urinary Infections*

Rapidly recurrent stones tend to be pure and relatively unmixed and of the same composition as their predecessors

**B Blood chemistry studies—**

Blood uric acid—serum calcium—blood phosphorus (Repeat several times)

**C Uricate calculi—Low purine diet\*—**

Intense alkalinization of urine.

**Calcium oxalate calculi—**

Low oxalate dietary\* Intense acidification of urine Give Vitamins B and D to decrease oxaluria

Calcium oxalate is precipitated in a wide range of urinary reaction Best solution is maintained at pH 5.2, poorest at pH 6.1 (Maslow) This is most difficult stone to dissolve or to control by urinary reaction

**Calcium carbonate and calcium or ammonium magnesium phosphate calculi**

Low phosphate dietary\* (Especially avoid milk and dairy products Probably high acid ash diet better)

Intense acidification of urine (pH 4 to 5)

**Cystin calculi—**

Intense alkalinization of urine

\*An excellent series of diets are listed in an article by Grant and Simpson—Southern Medical Journal—July 1930 Also consult Barborak Treatment by Diet, Lippincott, 1934

**D To acidify urine—ACID ASH DIET—(see next page)**

Dilute nitrohydrochloric acid (aqua regia)

**R** Conc nitrohydrochloric acid

10 cc

Distilled water q s

100 cc

Sig Take 1 drachm in 1 glass water q 1 to 2 hrs to tolerance Sip through tube and rinse mouth with sodium bicarbonate solution after taking Care not to swallow bicarbonate solution

**Or Use ACID DIURETIC MIST****R** Ammonium benzoate

Dr II

Ammonium chloride

Dr III

Ammonium nitrate

Dr III

Saccharose

Oz IV

Elixir of Lactated Pepsin q s

Oz VIII

N B—Mix in mortar to syrup

Sig Drachms one to two in glassful water every

one to two hours unless nauseated

Each drachm contains 0.5 gm of acidifying drug

This syrup is usually well tolerated and has been found the best urinary acidifier in our experience It may be used together with—

Enteric coated tablets—Ammonium Chloride—  
6 to 10 gms dailyEnteric coated tablets—Ammonium Nitrate—  
6 to 10 gms daily

Watch stool to be sure enteric coated tablets are absorbed

The use of the acid diuretic mixture dilute aqua regia enteric coated tablets and acid ash diet singly or simultaneously has generally been well enough tolerated to render acid resistant urinary alkalinity If patient is nauseated omit one or two doses and continue When 8 to 10 gm acidifying drug are exceeded in 24 hours watch for systemic acidosis Certain types of urea splitting organisms e.g. proteus and some staphylococci defy urinary acidification Acid urine is possibly secreted, but is at once alkalinized by bacterial action

**LACTIC OR HYDROCHLORIC ACID MILK** (10 to 60 drops of lactic or dilute HCl to 6 oz boiled milk)—  
1 glass 4 times or more daily Useful in infants and children**E To alkalinize urine—ALKALINE ASH DIET—see next page****ALKALINE DIURETIC MIST****R** Kali citratis

Oz I

Sodii bicarbonatis

Dr IV

Syr Orange

Oz IV

Aqua Dist q s

Oz VIII

Sig Drachms III in water a.c. and h.s

Magnesia, potassium citrate or acetate, sodium bicarbonate in suitable prescription

**F TO TREAT THE URINARY TRACT INFECTION—****SMEARS AND CULTURES at Initial Urologic Examination**

Study voided and catheterized bladder urine, catheterized ureteral specimens from each kidney determining pH on usual dietary

Differentiate infectious organisms by laboratory methods (Gram stain simple and useful)

**NEOARSPHENAMINE**—0.2 gm intravenously followed in 5 to 7 days by 0.3 gm

Frequently of value in staphylococcus and streptococcus fecalis Do not continue if first two doses show no improvement

Use cautiously in acute infections and with renal insufficiency

**METHENAMINE**—Keep urinary reaction below pH 5.6 Push dosage to tolerance 4 to 8 gm daily Watch urine for increase in red cells or casts Do not continue large doses over long period Drop maintenance dose to 3 to 4 gm daily If not effective after several days do not continue If given intravenously calculate amount in total daily dosage**ACRIFLAVINE—CAPROKOL—AZO DYES** (Pyridium Serenium etc.) Seldom sterilize urine but good bacteriostatics and reduce infectionor 0.04 percent chlorophenol red—1 drop to 20 drops urine { Red—pH 5.2  
or Nitrazene Paper { Green—pH 5.5  
— Patient May Be Taught To Use These —

**KETOGENIC DIET**—References—Clark, A L J A M A 107 1280 1284-1936 Nesbit, R M J A M A 105 1183 1114, 1935

Not well tolerated in many patients Used less frequently now as mandelic acid in most instances affects same organisms more successfully and is better tolerated Bacillary and streptococcus fecalis infections respond best, coccal infections poorly except at times in lower urinary tract

**MANDELIC ACID**—Has largely replaced ketogenic diet Keep urinary concentration high by restricting fluids to 1000 to 1500 cc daily (except in acute cases) Keep pH by acid ash diet and drugs at pH 5.2

Give 12 gm mandelic acid daily to adults (as sodium mandelate or ammonium mandelate) Infants and children according to age Do not continue over two or three weeks and examine urine carefully for appearance or increase of red cells and casts In cases of renal insufficiency take care not to produce acidosis Watch for nausea vomiting hyperreflexia and check CO<sub>2</sub> combining power of blood

**SULFANILAMIDE**—In urinary tract effective for bacilli including proteus Does not affect cocci so well Streptococcus fecalis does not respond

Active (probably most active) in alkaline urine Keep pH at 7.5 or higher Develops bactericidal urine in renal insufficiency At present oral administration appears equally or more effective than intramuscular or intravenous route Secreted in poor concentration in prostatic secretion but very effective in prostatic infection Dosage not standardized—Start with 60 to 80 grains daily in four doses Reduce to 40 grains daily after 2 or 3 days

Watch tolerance of patient and for many bizarre untoward reactions—Progressive cyanosis hemoglobinuria hematuria hyperpyrexia, leucopenia agranulocytosis erythraemia dermatitis anemia jaundice and reinitis indicate discontinuance of drug Usually prompt recovery from toxic symptoms ensues Do not give any type of sulphates and especially avoid magnesium sulphate during sulfanilamide administration Watch patient daily

**REDUCE FOCAL INFECTIONS**—teeth—tonsils—prostate—cervix—alimentary tract

**SURGICAL DRAINAGE**—Nephrostomy—Seminal Vesiculotomy—Cystostomy—Removal of prostatic obstructions—Suspension of kidney etc—when indicated

**UROLOGIC DRAINAGE**—Indwelling catheters—Periodic cystoscopic ureteral dilatation Dilatation of small calibered urethra Valuable measures if applied gently and increasing size of dilator gradually Avoid trauma

Lavage with 1 to 2% phosphoric acid etc Continuous irrigation with acids by any method is not tolerated by most patients and may provoke severe reactions Of value chiefly in post operative effort to prevent recurrence of stone

#### SUMMARY

Surgical removal of stone usually indicated when possible Adjust urinary reaction in accordance with chemistry of stone Correct metabolic error—hyperparathyroidism uric acid oxalate phosphate hyperexcretion Reduce infection For coccal infection use neosphenamine and methenamine For bacillary infections and streptococcus fecalis use urinary acidification and mandelic acid In alkaline bacillary infections use sulfanilamide Remove focal infection Establish drainage

Patients with bone disease (fractures infections, tumors, osteitis deformans osteitis fibrosa cystica) patients with spinal cord injuries or patients long bedridden—keep urine at acid range (pH 5 to 5.2) as prophylaxis against stone

**G Increase Vitamin A Intake**—Sources—Cod liver oil—Haliver oil—Carotene (Provitamin A)

#### FOODS—

APRICOTS	CHEESE	Oysters	Vegetables with green or yellow pigment as	
BEEF LIVER	(Am or Swiss)	Peaches	Asparagus	CRESS
Beef Fat	CREAM	Pineapples	Beans green	LETTUCE
BUTTER	EGG YOLK	Prunes	Cabbage	PEAS (green)
Bananas	Kidneys	Tomatoes	CARROTS	Peppers
Cantaloupe	Milk		Corn (yellow)	Pumpkins (yellow)
CHARD	Oranges			

#### ACID-ASH DIET

(Expressed in cc Normal reagent per 100 gm food)

This diet is deficient in Vitamin C For this reason Vitamin C vegetables of low alkaline ash content may be added locally if the patient is on the diet for a long time

Egg yolk	27	Pork lean	10	Crackers soda	83	Bread (rye)	
Oysters	151	Veal loin	98	Pork chops	8	Corn Meal	
Macaroni	143	Ham smoked	97	Walnuts	78	Peanuts	
Shredded Wheat	122	Sponge Cake	90	Bread whole wheat	73	Corn green	
Whole Wheat	12	White Flour	90	Bread white	71	Cranberries Plums	
Oatmeal	12	Beef ribs lean	96	Perch	63	including Prunes	
Sardines	113	Mutton leg	96	Corn, (dry)	59		
Eggs whole	11	Soy bean Meal	95	Cheese Cheddar			
Beef porterhouse steak	109	Rice	93	(American)	54		
Chicken	107	Halibut fresh	93	Egg White	52	NEUTRAL	
Salmon canned	107	Flour white	90	Lentils	51	Tapioca	Lard
Barley pearl	104	Trout salmon	88	Swiss Cheese	5	Butter	Sugar
Beef Liver	105	Cod fish	84	Bacon	5	Cream	Cornstarch
						Oil	

#### ALKALINE-ASH DIET

(Expressed in cc of Normal reagent per 100 gm food)

Molasses	56	Citron	96	Bananas—C	56	Raspberries—C	
Olives	456	Rutabagas—C	85	Oranges—C	56	Apples—C	
Dried Flgs	329	Rhubarb—C	85	Tomatoes—C	56	Pears fresh	
olives	270	Cucumbers—C	79	Peas fresh string	54	Radishes—C	
	236	Celery—C	78	Condensed Milk	52	Watermelon—C	
dried	18	Cantaloupe—C	75	Evaporated Milk	53	Turnips—C	
Milk	18	Lettuce—C	74	Cauliflower—C	5	Milk whole raw	
	158	Potatoes white—C	7	Lemons—C	5	Buttermilk	
fresh luma	14	Cocconut	7	Pears (dry)	5	Onions—C	
Almonds	123	Pineapples fresh—C	68	Perches fresh—C	5	Pumpkins—C	
Parsnips	12	Sweet Potatoes—C	67	Chestnuts	5	Peas fresh—C	
Dates	11	Cabbage—C	6	Cherries—C	45	Asparagus—C	
Beets fresh	109	Baked Beans	6	Mushrooms	4	Grapefruit—C	
Carrots—C	108	Apricots	6	Grape Juice	4	Ice Cream	
Figs	10						

C signifies high Vitamin C content

## SOFT ACID ASH DIET

ay have the following foods

EGGS (poached soft boiled soufflé egg custard shirred creamed omelet scrambled)  
 MACARONI (creamed buttered or cooked in chicken stock)  
 COOKED CEREALS (rice and grits may be served as vegetables or cereals and oatmeal cream of wheat, farina and wheatena also cornmeal as mush)  
 CRACKERS  
 BREAD (whole wheat rye and white)  
 CORN (green or canned either very tender or run through sieve to remove outer skin)  
 DESSERTS (custard rice puddings tapioca custard bread puddings—made with eggs and one half milk and one-half 20% cream)  
 CHICKEN (stewed creamed or baked)

ater may have

Fresh halibut boiled broiled or baked  
 Fresh trout boiled broiled or baked  
 FRUITS (cranberries plums (cooked) and prunes (may be combined with eggs as whips or soufflés)  
 NEUTRAL FOODS (cream butter tapioca sugar, cornstarch)

## AMPLE MENU FOR DAY

BREAKFAST	LUNCH	DINNER
Prunes with cream	Cream of chicken soup	Bouillon with toasted
Oatmeal shredded wheat	with crackers	crackers
with cream	Egg omelet	Stewed chicken with
Poached egg on toast	Buttered grits	gravy
Toast with butter	Stale muffins (toasted	Steamed rice
Coffee or tea with cream	with butter)	Stewed corn
and sugar	Prune whip (made with	Toast with butter
	stiffly beaten egg white	Baked chocolate custard
	pureed prunes and sugar)	Coffee or tea with cream
	Coffee or tea with cream	and sugar
	and sugar	

## SOFT ALKALINE-ASH DIET

FRUITS ALLOWED—(all fruits on list)—  
 Orange juice pineapple juice grapefruit juice tomato juice, peach juice apricot juice pear juice  
 Baked apple without skin baked pear without skin fresh or canned applesauce canned peaches pears  
 apricots Royal Anne cherries  
 VEGETABLES on alkaline list—  
 All vegetables must be strained Carrots peas lima beans butter beans string beans tomatoes asparagus  
 spinach beets squash baked potato or mashed potato  
 MILK AND MILK PRODUCTS ALLOWED—  
 Sweet or buttermilk, cottage cheese cream butter  
 Any ice cream without solid fruits or nuts  
 Chocolate milk or hot chocolate  
 BREADS ALLOWED—  
 Toast (white or brown) NOT MORE THAN ONE AND ONE HALF SLICES EACH DAY  
 EGGS—Do not eat more than ONE egg a day  
 DESSERTS (BESIDES FRUITS) ALLOWED—Simple puddings made with any of the allowed fruits—Baked custards tapioca puddings  
 COFFEE AND TEA—MAY BE TAKEN AS DESIRED  
 Sugar salt and pepper as desired

## AMPLE MENU FOR DAY

BREAKFAST	LUNCH	DINNER
Any allowed fruit or	Cream or vegetable	Fruit cup
fruit juice	soup	Mashed potato
One egg	Baked potato	Vegetable purees
Milk	Vegetable purees	$\frac{1}{2}$ slice toast.
Coffee or tea.	$\frac{1}{2}$ slice toasted bread	Milk.
$\frac{1}{2}$ slice bread (toasted)	Milk.	Dessert.
	Allowed fruit or dessert	
	or both	

## NOTES ON SOFT ALKALINE-ASH DIET

In keeping a diet alkaline—eggs which are one of our most valuable sources of protein in the soft diet must be very limited so in order to keep the body built up a great deal of milk should be consumed  
 The patient should take at least  $1\frac{1}{2}$  quarts of milk each day This may be used in soups specially prepared drinks or may be taken plain  
 Notice that none of the foods allowed are limited in amounts except eggs and toast These are limited because they contain acid properties



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## PROCEEDINGS OF ACADEMY MEETINGS

### STATED MEETINGS

JANUARY 6—*The New York Academy of Medicine Annual Meeting* Executive Session—a] Reading of the minutes, b] Presentation of diplomas ¶ Presentation of annual reports (read by title), The Council, The Trustees, The Treasurer, Committees ¶ Report of the Fund Raising Committee, Shepard Krech ¶ Address of the President, James Alexander Miller, the significance of The New York Academy of Medicine ¶ Report on election of members

JANUARY 20—*The Harvey Society in affiliation with The New York Academy of Medicine* The fourth Harvey lecture, "Transfers of Water and Solutes in the Body," John P Peters, Professor of Medicine, Yale University

### SECTION MEETINGS

JANUARY 4—*Dermatology and Syphilology* Reading of the minutes ¶ Presentation of cases—a] Vanderbilt Clinic, College of Physicians and Surgeons, b] Miscellaneous cases ¶ Discussion of selected cases ¶ Executive session

JANUARY 7—*Surgery* ¶ Reading of the minutes ¶ Presentation of cases—Two cases to illustrate each paper of the evening ¶ Papers of the evening—a] Surgery in the treatment of advanced cancer of the

lip, Hayes E Martin, Discussion, Jerome P Webster, b] Common carotid artery ligation in head and neck cancer, William L Watson, Discussion, John M Hanford, c] The use of the actual cautery in the treatment of carcinomas of the head and neck, William S MacComb (by invitation), Discussion, William F MacFee ¶ General discussion ¶ Executive session

JANUARY 11—*Combined Meeting, Section of Neurology and Psychiatry and The New York Neurological Society* Presentation of cases—Two cases demonstrating allergic reactions in the central nervous system, Irving Pardee ¶ Papers of the evening—a] Allergy and its effect on the central nervous system, Foster Kennedy, Discussion, Angus Frantz, Robert A Cooke, Israel Wechsler, b] Sulfanilamide in the treatment of acute infections of the central nervous system, Josephine B Neal, Discussion, Emanuel Appelbaum, Clarence C Hare ¶ Executive session

JANUARY 12—*Historical and Cultural Medicine* Reading of the minutes ¶ Papers of the evening—a] Sidelights on the history of medicine in Spain and Portugal, Harry Friedenwald, Baltimore (by invitation), b] Hieronymus Münzer and other Fifteenth Century Bibliophiles, E P Goldschmidt, London (by invitation). ¶ General discussion ¶ Executive session

JANUARY 13—*Pediatrics* Program presented by members of the Department of Pediatrics of the University of Pennsylvania Medical College ¶ Papers of the evening—*a*) Curd size and curd tension of milk, Irving J Wolman (by invitation), Leslie A Chambers (by invitation), Discussion Logan F Wilson (by invitation), Plunshoro, N J *b*) Some observations on hypertension in acute glomerulonephritis Mitchell I Rubin (by invitation), Milton Ripoport (by invitation) Discussion John D Lyttle, *c*) The effect of the maternal diet upon resistance to infection, Charles F Church (by invitation) Discussion, Leslie I Webster (by invitation) *d*) The velocity of spread of nasopharyngeal infection, W F Wells (by invitation), M Wells (by invitation), *e*) Studies on influenza, Joseph Stokes, Jr (by invitation), Dorothy R Shaw (by invitation), Athol S Kenney (by invitation) Discussion of papers *d* and *e* by Thomas Francis Jr

JANUARY 17—*Ophthalmology* Instructional Hour—Diseases of the cornea, Bernard Samuels, Edward B Burchell (by invitation) ¶ Slit Lamp Demonstration, Milton L Berliner, Wendell I Hughes, Girolamo Boniccolto, Gordon M Bruce ¶ Reading of the minutes ¶ Presentation of cases—*a*) Simple operation for spastic entropion, Sigmund A Agatston, *b*) Comparison of operations for paralysis of the external rectus, Brittain F Payne ¶ Paper of the evening—Anomalous projection and other visual phenomena associated with strabismus, Frederick H Verhoeff (by invitation)

JANUARY 18—*Medicine* Reading of the minutes ¶ Papers of the evening—*a*) The present knowledge of vitamin requirement in man, Henry C Sherman, Mitchell Professor of Chemistry, Columbia University (by invitation) Discussion, R R Williams (by invitation), I Ogden Woodruff, *b*) Pathological responses to vitamin deficiencies, Gilbert Dilldorf (by invitation), Discussion, C P Rhoads ¶ General discussion

JANUARY 19—*Genito-Urinary Surgery* Reading of the minutes ¶ Presentation of cases—Three cases of tuberculous meningitis following nephrectomy, G Aubrey Hawes (by invitation) ¶ Paper of the evening—Renal tuberculosis in patients with active pulmonary tuberculosis, Edwin M Jameson, Sarinac Lake (by invitation) ¶ Discussion, Edwin Beer, George F Cahill, Thomas J Kluwin

JANUARY 19—*Otolaryngology* Reading of the minutes ¶ Presentation of cases—Cases of cancer of larynx treated by radiotherapy, Maurice Lenz ¶ Report of cases—*a*) Salivary fistula, following mastoid operation Two cured cases, E B Bilschick (by invitation), *b*) Chondroma of the bronchus Report of two cases, A J Cracovaner *c*) An unusual case of epithelioma of the nasopharynx, G E Bradford (by invitation), *d*) Multiple myeloma of the temporal bone F P Fowler, Jr (by invitation), *e*) Epistaxis from telangiectases, treated by quinine urethane injection, G H O'Kane (by invitation) *f*) Traumatic rupture trachea, George Worcester (by invitation) ¶ Papers of the evening—*a*) Foci of infection in rheumatoid arthritis, R I McCollom (by invitation), *b*) A new double bronchoscope, G R Brighton *c*) A critique of the treatment of laryngeal cancer, J D Kernan, Discussion by R E Buckley, M Lenz ¶ General discussion The cases presented were chiefly from the Service of Prof John D Kernan at Presbyterian Hospital, Babies Hospital and Vanderbilt Clinic

JANUARY 25—*Obstetrics and Gynecology* Papers of the evening—*a*) Treatment of pelvic inflammation by iontophoresis of a choline compound, Adolph Jacoby, Discussion, Walter T Dannreuther, Irving S Wright, David N Barrows, *b*) Management of the third and fourth stages of labor, Morris Leff Discussion, William E Caldwell, Alfred C Beck, William E Studdiford, John B Pastore, *c*) The problem of the after-coming

head, Robert J Lowrie, Discussion, James P Hennessy, Claude E Herton

*Orthopedic Surgery* Notice—On account of the meeting of the American Academy of Orthopedic Surgeons at Los Angeles this month, no meeting of the Orthopedic Section at the Academy was held

### AFFILIATED SOCIETIES

*New York Roentgen Society* The Annual Roentgenological Conference of the Eastern Societies was held in Philadelphia January 28 and 29, and took the place of the regular January meeting of the New York Roentgen Society

JANUARY 27—*New York Pathological Society in affiliation with The New York Academy of Medicine* Case Reports—*a*] Masculinization associated with an ovarian tumor (luteoma vs hypernephroma), Antonio Rottino, *b*] Cystic lymphangiectasia of the adrenal, S Milton Rabson, Edward F Zimmerman (by invitation), *c*] Three interesting carcinomas arising in the biliary tract, L H Meeker, George Savyol (by invitation), *d*] Ulceration of peritoneum (chemical?), L H Meeker, J M Gannon (by invitation), *e*] Carcinoma (metastatic) and coexisting acute appendicitis with perforation, L H Meeker, S R Weinberg (by invitation) ¶Papers of the evening—*a*] General observations on the serum therapy of infections with streptococcus, Adele E Sheplar (by invitation), Martha Jane Spence, M A (by invitation), Ward J MacNeal, *b*] Further observations on bacteriophage action in the presence of blood, Ward J MacNeal, Margaret A

McRae, B S (by invitation), Rudolph A Colmers (by invitation) ¶Slide Demonstrations—*a*] Phagocytosed staphylococci in the circulating blood, E H Pahl, B S (by invitation), Ward J MacNeal, *b*] Differentially stained particles within bacteria undergoing lysis by bacteriophage, Ward J MacNeal, Frances C Frisbee, A B (by invitation) ¶Executive session—Election of officers

JANUARY 19—*New York Section of the Society for Experimental Biology and Medicine* The path of escape of vital dyes from the lymphatics into the tissues, Philip D McMaster, Robert I Parsons (by invitation) ¶Differences in the temperature of the skin and muscles of the lower extremities following various procedures, Mae Friedlander, Samuel Silbert, William Bierman, Norman Laskey (Introduced by Gregory Schwartzman) ¶The effect of kidney retention and other factors on the excretion of vitamin C after an intravenous dose of ascorbic acid, Irving S Wright, Elizabeth MacLenathen ¶Reversed iontophoresis of histamine from human skin Its bearing on the histamine theory of the allergic wheal H A Abramson, M Engel (by invitation), V Lubkin (by invitation), I Ochs (by invitation) ¶The effect of pH on the metamorphosing action of the thyroxine upon tadpoles, S H Rosen (Introduced by D Perla) ¶The fate of tubercle bacilli in sensitized and in immunized animals, Jules Freund, D Murray Angevine (by invitation) ¶The reticulo-endothelial system and the concept of the "anti-hormone," Albert S Gordon (by invitation), William Kleinberg (by invitation), Harry A Charipper

BULLETIN OF  
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MARCH 1938

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CLINICAL ASPECTS OF CALCULUS DISEASE\*

HENRY G BUGBEE

Attending Urologist St Luke's Hospital

ONE FINDS in the more recent urological literature many contributions relative to calculus disease. These articles deal largely with the etiology of stone formation and its correlative subject, the prevention of recurrence. To the urologist, at the present time, this is probably the most important and interesting phase of the subject. Much of the knowledge gained by these researches, however, must still be classified as theoretical, and a true evaluation can only be made after further investigations have been carried out, especially along the lines of chemistry, bacteriology, and body metabolism.

The clinical aspects of lithiasis is a broad subject indeed, and one which obviously can only be touched upon in the limited space allotted. To form the basis for these observations (which are directed primarily to those practicing in fields other than urology, especially the general practitioner), I have briefly reviewed cases of calculus disease that have been under my observation in hospital and private practice during the past six years, and attempted to elicit certain points in the clinical histories which would be of greatest interest.

During these years we have been able to utilize all of the most modern

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\* Delivered November 9, 1937, in the Tenth Annual Graduate Fortnight.

methods of urological diagnosis, which have been particularly efficacious in the study of lithiasis, we have also worked in the light of our modern conception of the etiology of stone formation

In order of frequency, calculi have been encountered most often (1) in the ureter, (2) kidney, (3) bladder, (4) prostate, and (5) urethra. That the greatest incidence of calculi is to be found in impacted ureteral calculi is not surprising. The majority of all calculi are formed in the kidney, and while still of a size sufficiently small to make it possible, descend into the ureter and become impacted, where as a rule they give rise to symptoms of sufficient severity to focus attention upon their presence and result in their detection.

The alertness exhibited by the general practitioner in suspecting the possible presence of a ureteral calculus with the first appearance of suggestive symptoms, is an agreeable commentary upon more recent urological teaching. I well recall hearing Dr. C. H. Mayo make the statement years ago, that practically every patient coming to the Clinic with a right ureteral stone had already had the appendix removed, and often in the presence of a left sided calculus, the pain in the latter instance being interpreted as referred pain.

One cannot say that such instances do not occur even in this enlightened period, but they are much less common. A sudden severe pain in the flank, side or groin is now looked upon with suspicion by both physician and surgeon, and an x-ray is usually taken. If, as often happens, urinary symptoms are also present, and pus, blood cells, and possibly crystals are found in the urine, the diagnosis of lithiasis will soon be made. On the other hand, a predominance of gastro-intestinal symptoms and a high blood count, so commonly encountered in cases of acute appendicitis, will frequently exclude the possibility of a calculus. Formerly the appendix was removed at once, and a persistence of symptoms attributed to the presence of adhesions, by the time a correct diagnosis was finally made, an unnecessary operation had been carried out and much time lost. Today in hospital practice, with all facilities at hand, doubtful cases are seldom allowed to rest without a complete urological work up, including ureteral catheterization, retrograde and excretory urograms, and laboratory tests.

In many instances the clinical picture of impacted ureteral calculus is not typical, and may be confused with various types of acute pathology associated with the abdominal viscera, as well as chronic diseases of the

gallbladder, gastro-intestinal tract, or genital system. Symptoms relative to calculi are caused by obstruction, by local irritation, and by superimposed infection. If calculi lodge in the ureter and remain there without causing complete obstruction, they may attain an incredible size, as in several instances which came under my observation. Such large calculi often give rise to symptoms so slight that they remain undiagnosed for years. The term "silent stones" has often been applied in such cases. This term implies a certain false sense of security and lends comfort to the patient, while, even in the absence of pain and urinary symptoms, the calculus may be slowly causing kidney destruction, resulting in a progressive loss of function. Furthermore, the absence of a shadow in a plain film cannot be accepted as proof that a ureteral calculus is not present. It has been estimated by some, that as high as 10 per cent of ureteral calculi will not cast a shadow. While a pure uric acid stone may occasionally be missed, other methods of diagnosis such as a scratch on a wax bulb, or the presence of a filling defect when a contrast urographic medium is employed, should leave a much narrower margin of error.

While discussing ureteral calculi, I would like to call your attention to a phenomenon often referred to as passing gravel. An attack of pain quite typical of renal colic and often associated with gastro-intestinal symptoms, will be followed by hematuria, dysuria and urinary frequency. X-rays are usually negative, but the urine if examined repeatedly will show uric acid, or more often calcium oxalate crystals, possibly a visible sediment, also blood cells, and as a rule pus cells. When the bladder is examined, hemorrhagic areas are often observed in the mucous membrane of the trigone, bas-fond, and especially in the immediate vicinity of one or both ureteral orifices, which may also be surrounded by an area of edema. The lumen of the ureter may be free, or partially obstructed, frequently one is able, by means of lavage of the ureter, to wash out a sediment of crystals. These occurrences have been more often encountered during the spring and summer, and have seemed to be associated with gastro-intestinal disturbances in patients who have ingested large quantities of fresh vegetables and fruits high in calcium content. All have presented a clinical picture so clear cut, and have occurred with such regularity, that I am inclined to believe that these observations regarding the etiology of this type of case are well founded.

It has been estimated that probably 40 per cent of all ureteral calculi will pass without instrumentation. Statistics have also shown that another



40 per cent will pass following intra-ureteral manipulation. Here again, as in all urological work, application of the proper treatment should be based upon the several findings in the individual case, rather than being guided only by the size and position of the calculus. Surprisingly large calculi often pass following very little manipulation, while very small stones may resist repeated efforts to dislodge them. Just what happens to a calculus following an attack of colic, the number of colics, the presence or absence of urinary infection, the amount of back pressure upon the kidney and resulting interference with kidney function (as evidenced by the ureteral and pelvic dilatation so well demonstrated by urograms and verified by estimations of blood chemistry) are important guides upon which a decision should be based as to whether intra-ureteral manipulation should be continued or a calculus should be removed surgically.

Intra-ureteral manipulation is not without risk. Traumatism inflicted by such maneuvers may lead to stricture formation, and predispose to infection, the latter, when superimposed upon a kidney subjected to back pressure, may result in serious damage to the kidney, ending in a nephrectomy. A clean-cut surgical removal of an impacted calculus may, in certain instances, prove to be the more conservative treatment. Certainly, gentleness in manipulation and repeated careful check-ups, especially of kidney function, are constant requisites when cystoscopic methods are being employed.

A series of 114 ureteral calculi under treatment since 1931 showed twenty-two removed by uretero-lithotomy, ninety-two passed following intra-ureteral manipulation, with no mortality. Two patients are still undergoing manipulations, and as yet have resisted repeated attempts to dislodge the calculi. Once a calculus has descended through the ureter, seldom is difficulty encountered in its passage from the bladder. If not expelled at once, small stones may be removed by cystoscopic methods.

As has been stated, a large percentage of urinary calculi form in the kidney and pass into the ureter. A certain number, however, will remain attached to a papilla, or in a calyx, or in the kidney pelvis, until they reach a size which prohibits their passage into the ureter. If a calculus becomes impacted at the ureteropelvic junction, a renal colic will ensue which will not be relieved until the stone becomes dislodged. Calculi lodged in a calyx or minor calyx may give rise to a dull pain in the loin, but seldom to a sharp colic, stones not infrequently remain in a kidney



Fig 1

Prostatic calculi Symptoms relieved by treatment

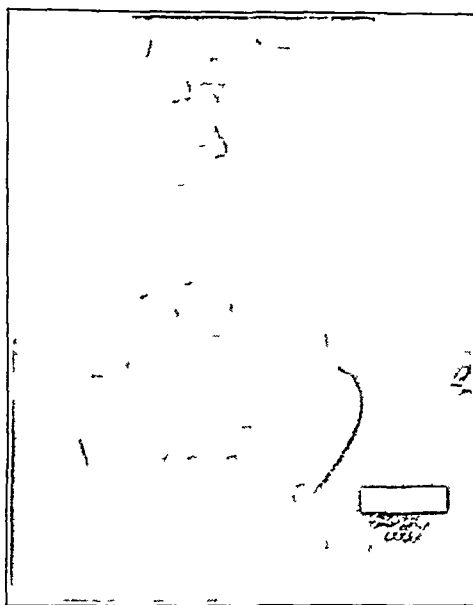


Fig 2

Vesical calculi Suprapubic cystotomy and prosta-  
tectomy



Fig 3

Vesical calculi Litholapaxy and transurethral  
resection



Fig 4

Jack-stone vesical calculus Litholapaxy



Fig 5

Calculus in vesical diverticulum. Lithotripsy and transurethral resection



Fig 6

Large vesical calculus



Fig 7

Same case as Fig 6. Urogram shows pelvic kidney also



Fig 8

Calculus in either ureter, also multiple calculi in both kidneys. Ureteral calculi passed following manipulation



Fig 9

Five ureteral bougies in ureter. Calculus passed subsequently.

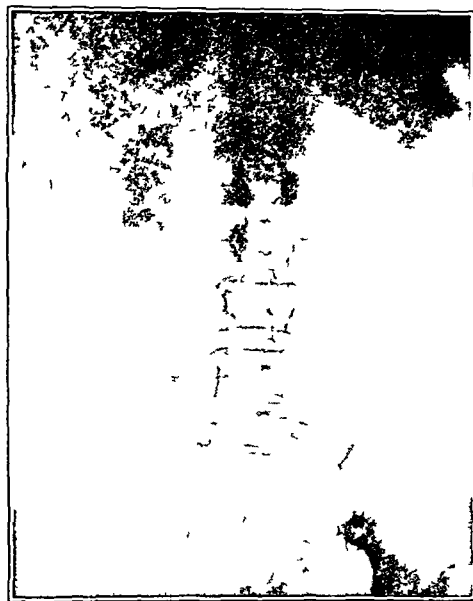


Fig 10

Impacted ureteral calculus. Excretory urogram shows dilatation of ureter above the calculus. Calculus passed following manipulation.

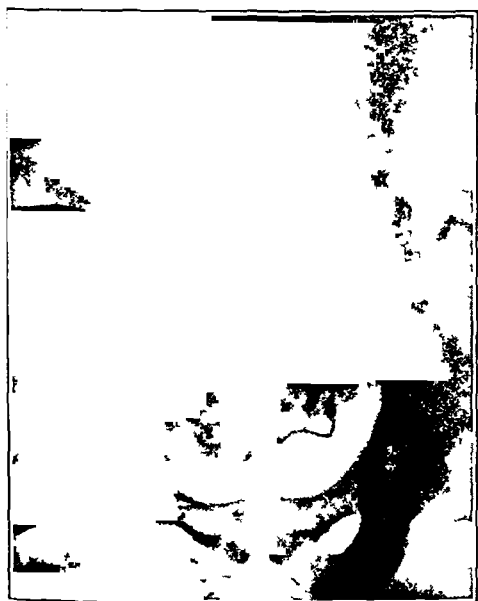


Fig 11

Impacted ureteral calculus. Ureterolithotomy.

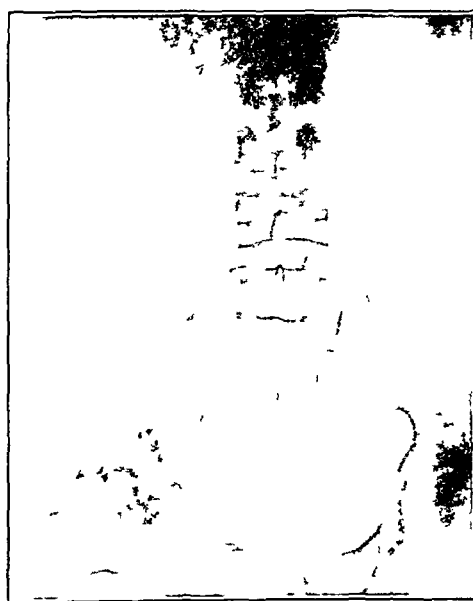


Fig 12

Calculus impacted in single ureter. Passed following manipulation.



Fig 13

Giant ureteral calculus No acute symptoms Ureteronephrectomy



Fig 14

Giant ureteral calculus No symptoms Ureterolithotomy

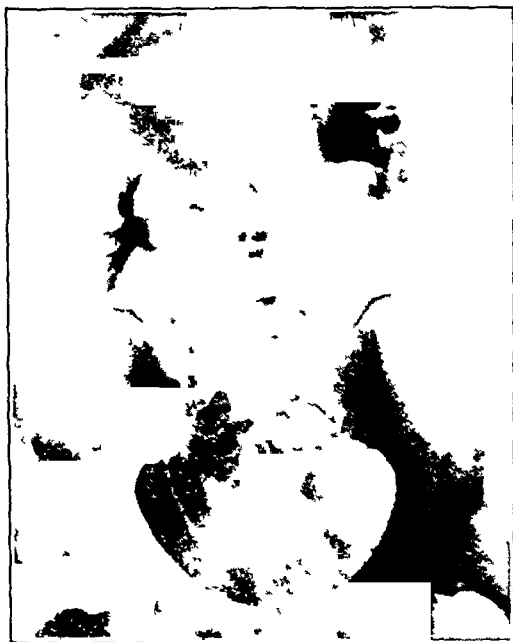


Fig 15

Hydronephrosis secondary to long continued ureteral obstruction from calculus

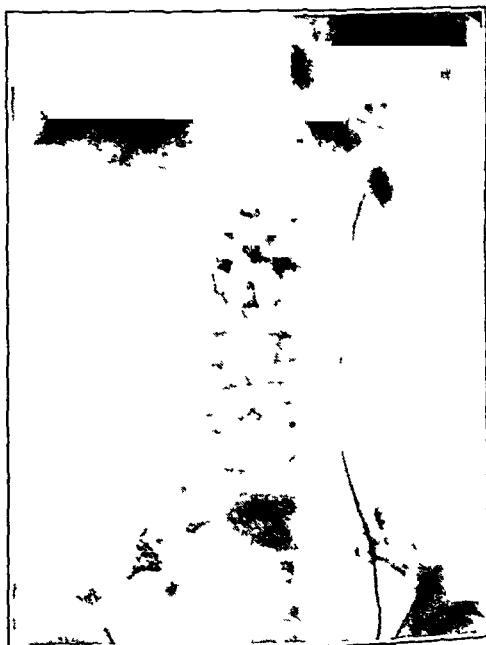


Fig 16

Calculus in right ureter and left kidney Ureterolithotomy and pyelonephrotomy



Fig 17

Filling defect in left kidney due to presence of uric acid calculus

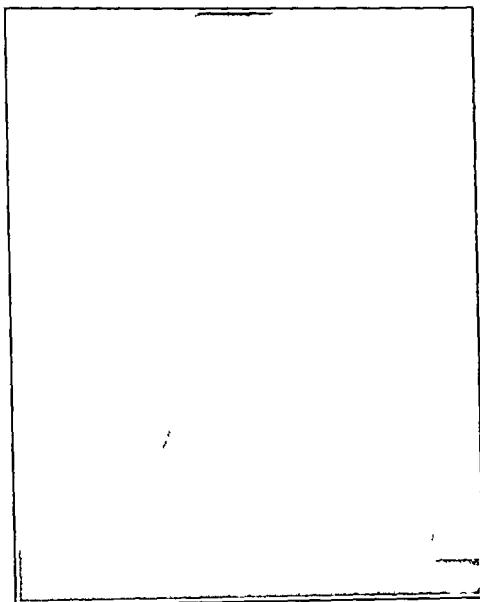


Fig 18

Small calculus in right kidney. Pelviolithotomy and plastic operation on kidney pelvis

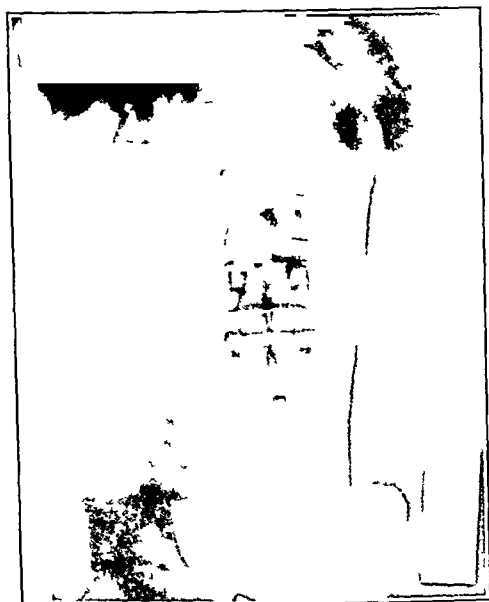


Fig 19

Renal calculus and ruptured kidney

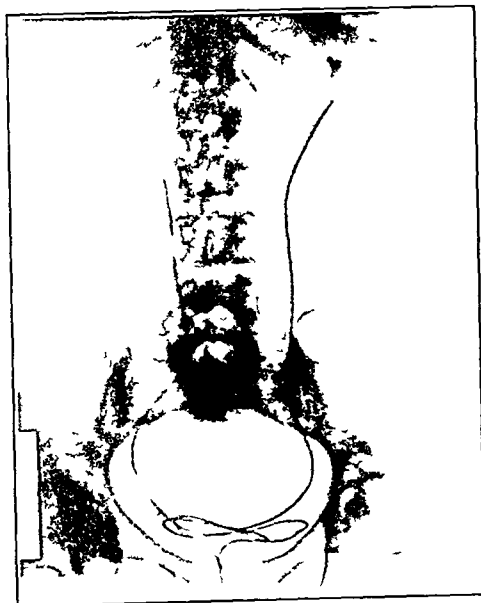


Fig 20

Renal calculus



Fig 21

Same case as Fig 20 Rupture of kidney with perinephritic abscess

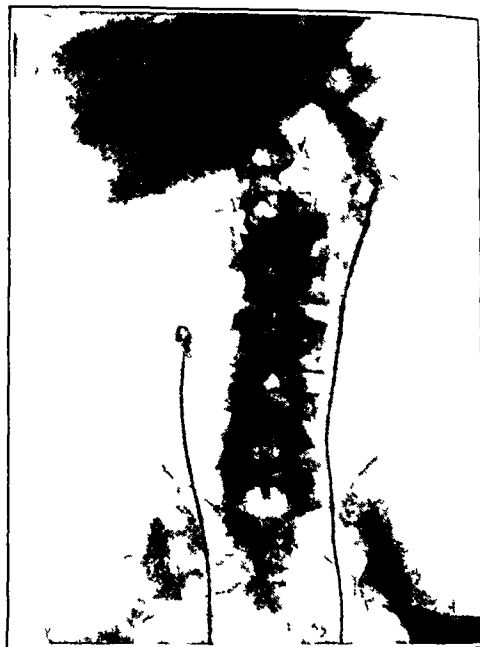


Fig 22

Renal calculus

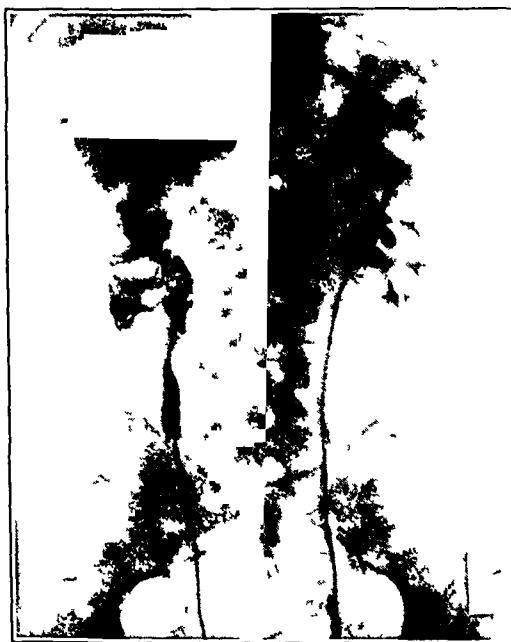


Fig 23

Same case as Fig 22 Destruction of kidney parenchyma secondary to calculus obstruction Nephrectomy



Fig 24

Renal calculi observed over a period of 20 years with slight increase in size

until they attain a size sufficient to fill the entire pelvis and calyces causing little more than a dull ache, possibly no pain at all

It has been surprising to me, in reviewing forty-nine cases of kidney stones treated during this period, to note in how many instances, without a preexisting suspicion of their presence, renal calculi were detected in x-rays taken as part of a routine examination to determine the cause for abdominal symptoms, or for the presence of pus and blood cells in the urine

Calculi have been found more often in kidneys subject to some interference with drainage, either mechanical, anatomical, or pathological. Multiple calculi occurred more often in the presence of urinary infection. Bilateral calculi were present in eleven cases, in four of which no operation was carried out, while in seven, both kidneys were incised, an interval being allowed to elapse between operations. Obviously conservative surgery is an important requisite when bilateral calculi are under consideration. That over one-third of all operations for renal calculi required a nephrectomy, is proof of the destruction of tissue that may result secondary to the presence of lithiasis, and emphasizes the danger of regarding calculi as innocent or harmless even in the absence of symptoms.

Surgery may be contra-indicated in certain instances of calculus disease. In rare instances I have observed stag-horn calculi, also single or multiple calculi, that have remained in a kidney for periods of years, apparently giving rise to no untoward results. The presence of calculi should, however, be regarded as a potential hazard to the individuals who harbor them, and such individuals should be subjected to periodic examinations. Of forty-nine kidney operations for renal stone during the period from 1931, seventeen required nephrectomy, eleven nephrolithotomy, and nineteen pelviolithotomy, with no operative mortality.

A combination of renal and ureteral stones has been frequently encountered, in three instances calculi were present in both kidneys and both ureters. The management of such cases calls for the best of surgical judgment. The migration of kidney and ureteral calculi necessitates an x-ray of all patients harboring stones of small size immediately preceding operation. In the presence of multiple calculi, an x-ray of the kidney before the patient leaves the operating table is an important safeguard.

Vesical calculi are, in most instances, primarily renal calculi that have descended into the bladder and, owing to the presence of some path-



ology in that organ which interferes with its complete emptying (most often prostatic obstruction or a diverticulum), remain in the bladder to increase in size. Where there is urinary retention and alkaline decomposition, calculi may form primarily in the bladder, incrustations are also frequently associated with tumors of the bladder. Vesical calculi are rarely found in the female, and when present, have as a rule a foreign body as a nucleus.

It is difficult to believe that vesical calculi could, in the light of present methods of diagnosis, be overlooked and remain in the bladder to attain large size, and yet in this recent series in which twenty-three bladder stone cases are included, twelve varied in size from that of an English walnut to a hen's egg. Regarding their composition, an occasional stone may be nearly pure uric acid or calcium oxalate, but a lamellated structure is more commonly found in which phosphates and carbonates are mixed with the above.

Small vesical calculi give rise to more acute symptoms than larger ones, for the same reason that applies to renal calculi, i.e., small calculi, by engaging in the vesical orifice, are able to obstruct the outlet of the bladder more completely, and also, in moving about more freely they cause more irritation of the mucous membrane.

The early symptoms of stone in the bladder—frequency, urgency, hematuria and pyuria—are often attributed to prostatic obstruction. As a calculus increases in size, the symptoms may become less severe, and patients may go on for years with urgency and frequency by day when a plain x-ray film would reveal its presence. In fourteen of the twenty-three recent cases, the calculus or calculi were removed incident to a prostatectomy or prostatic resection, while nine others were successfully removed by litholopaxy or cystotomy.

Litholopaxy is an entirely satisfactory procedure when employed in suitable cases, and when carried out by one familiar with the technique. In the absence of traumatism, this operation results in a great saving of time to the patient. A preliminary transurethral resection may be advisable in one case, while in another the calculus may be crushed and evacuated, and a resection or prostatectomy employed as a subsequent procedure. Such manipulations require distinctly more skill for their execution than do open operations, the results, however, in properly selected cases, are brilliant. The kidneys frequently are subjected to a severe degree of back pressure from the presence of vesical calculi,

especially calculi of large size, caution is therefore necessary in the preparation of these patients for operation. Too sudden a relief of back pressure may result in uremia.

Prostatic calculi are encountered as small seed-like bodies (usually found at prostatectomy and located between the hypertrophied prostate and its capsule) or as definite calculi, usually multiple, and commonly composed of calcium oxalate. True calculi may be palpated as hard areas in the prostate, unless crepitus be elicited, they may easily be confused with carcinoma of the prostate. An x-ray, however, differentiates the two conditions at once.

Calculi may remain in the prostate for years and cause no symptoms, however, when infection supervenes, relief can seldom be obtained by any means short of a removal of the prostate. Of sixteen cases of prostatic calculi observed during this same period, eleven were treated by prostatectomy while five had symptoms of such a mild nature that they have been made comfortable by local treatment.

Urethral calculi (under which one excludes prostatic calculi that may have become dislodged) represent renal or vesical calculi which in their passage have become engaged in the urethra. One patient in this series suffered from six such impactions. The calculus in each instance was withdrawn with forceps. In two cases the calculus was pushed back into the bladder and removed with the cystoscopic rongeur. In another case an external urethrotomy was necessary for the removal of the stone.

A complete urological work-up of every case of lithiasis is necessary before deciding whether the treatment to be applied should be surgical, or whether cystoscopic manipulations are indicated, or in the presence of contra-indications to the above, whether one should depend upon medical measures in the hope of controlling the disease.

With the removal of a calculus, treatment has but begun. The elimination of urinary stasis is an important step, urinary infection should be eradicated, a familiarity with *all elements* entering into the etiology of stone formation is essential, that a proper regimen may be instituted, for only by such means may a recurrence be prevented.

The recurrences that I have encountered during the past six years have, with one exception, occurred in cases of multiple stones, one was in a case of bilateral single renal calculi, the composition of the stones being reported as pure calcium oxalate, a second was in a case of multiple bilateral renal oxalate stones, a third had multiple renal and ureteral

calculi composed of calcium and magnesium phosphate, and a fourth was a case of multiple vesical calculi composed of calcium oxalate and calcium phosphate (both of the latter had a strongly alkaline urine), a fifth case had a recurrence of a renal calculus of pure uric acid composition. In these cases every effort was made through the establishment of satisfactory urinary drainage, the elimination of foci of infection, increased elimination from the intestinal tract, the employment of a strict dietary regimen, supplemented by repeated studies of blood chemistry and metabolism, and local treatment of the kidneys by pelvic lavage to eliminate all constitutional and local factors which might predispose to calculus re-formation.

In the cases presenting recurrent oxalate and uric acid calculi constipation was a predominant predisposing factor which was difficult to relieve. Each of these cases continued, notwithstanding the above measures, to show calcium oxalate crystals in the urine. One case was lost to observation after six months of treatment, still harboring a recurrent renal calculus of increasing size. Two were reoperated (one twice), but have been free from further recurrence for three and four years respectively, although one still shows oxalate crystals in the urine from time to time. The two cases of multiple phosphatic stones were reoperated, one by cystotomy and the second on the opposite kidney and both ureters. They have now been free from calculi for two and four years respectively, although intermittently they both show triple phosphate crystals in the urine. Acidification of the urine has not always been possible. However, sulfanilamide has been of decided value in eliminating the proteus infection so often present in these cases. Dissolution of calculi, except in one case of cystinuria observed eighteen years ago, has not been observed.

In concluding these remarks I wish to emphasize the necessity of being ever alert to the possible presence of a calculus as a cause for urological or general symptoms, whether clear-cut or vague, or as an etiological factor in pyuria and hematuria, that every case presenting suspicious symptoms, or pus, blood, or crystals in the urine should at least have a plain x-ray film, that the presence of a calculus is always a liability to the individual who harbors it, and that the best of judgment, based upon a complete urological and general physical work-up, is necessary to apply proper treatment intelligently and prevent a recurrence.

## EDEMA AND ITS TREATMENT\*

DANA W. ATCHLEY

Associate Professor of Medicine College of Physicians and Surgeons

IT HAS been our good fortune in the last two or three decades to see many of the manifestations of disease subjected to genuine scientific analysis. Hitherto, classical clinical descriptions had merely enumerated these manifestations, designating them by the major diagnosis with which they were associated. Thus, we spoke of nephritic edema, cardiac edema or inflammatory edema. With the new analytic point of view it is necessary to discard this elementary identification and perform what may be called a physiological dissection, arriving thereby at the underlying mechanisms concerned in the production of edema in each individual case.

It is necessary, therefore, in discussing with you the problem of edema in nephritis to review the basic forces concerned in causing an increase of water in the intercellular spaces, i.e., edema. Time limitations prevent an exhaustive presentation of all the facts, hence I shall try to include only fundamental principles, first a brief exposition of the physiological equilibria whose alteration leads to edema formation, and then an analysis of the important types of Bright's disease for the presence of these alterations. Of necessity, such a program is further limited by constant collision with the barriers that still separate us from the unexplored fields of knowledge. It is only by comparison with the lack of understanding of twenty-five years ago, that the physician can indulge in a complacent attitude as to present knowledge.

The interstitial fluids are kept constant in the normal person by a remarkable balance between the *physical* pressure of the blood in the capillaries, derived primarily from the heart beat, and the *osmotic* pressure of the plasma, derived essentially from its proteins. This is the famous Starling hypothesis. Many careful investigations have proved that this hypothesis stands the test of quantitative analysis and that the exact figures for the two pressures expressed in equivalent terms, such as milli-

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meters of mercury, have the appropriate relationships. At the arterial end of the capillary, the physical pressure exceeds the osmotic pressure so that fluid moves out into the tissues, at the venous end of the capillary the osmotic pressure is increased by the concentration resulting from this loss of water and the physical pressure is decreased for similar reasons, so that fluid then passes back into the capillary. Experiments on animals have shown that the physical pressure on the arterial end is approximately twice that on the venous. The net result of this dynamic equilibrium between filtration and reabsorption is the maintenance (in the normal) of a constant water content in the intercellular spaces. Disease, however, can change either the capillary blood pressure or the osmotic pressure to such an extent that normal conditions cease to exist. Under these circumstances edema may then appear. Even in the normal, it is possible to cause slight edema of the ankles by standing over long periods of time adding thereby, the pressure of gravity to the normal capillary pressure.

Exact measurement of only one of these pressures is possible in the light of our present knowledge. This is the osmotic pressure, which can be determined by an estimation of the serum proteins. Factors are known whereby the percentages of albumin and globulin can be accurately translated into osmotic pressure as millimeters of mercury but the simple protein percentages are adequate for practical clinical use. The physician who is unaware of the necessity of such information in the treatment of edema, wherever it appears, is liable to many confused interpretations of his inadequate data. We shall return to this phase of edema when discussing nephrosis.

The hydrostatic pressure in the capillary is difficult to determine experimentally and almost impossible clinically. The nearest approach at the bedside is by means of inference based on the venous pressure. Although this may be on some occasions an ill-justified inference, particularly when the venous pressure is normal nevertheless few cases of edema can be thoroughly appraised without it.

Another important factor in the causation of edema is the state of the capillary wall. It is well-known that localized edemas such as those due to trauma, inflammation, or toxins are dependent upon an increase in the capillary pores with the consequence that an abnormal escape of plasma is permitted. Although this mechanism of edema formation is easily studied experimentally when it is due to local or external causes its role in general diseases, such as acute nephritis, is quite speculative and cer-

tantly lacking in well-proved facts. It has been assumed, with obvious justification, that edema fluid formed by the seepage of plasma through an overly permeable capillary membrane would have a higher protein content than that accumulating because of an alteration of the pressure relationships across a normal vessel wall. This assumption has been confirmed by analysis of the protein content of fluids accumulating in many types of experimental edema. When the underlying cause is a low osmotic pressure, the protein concentration is small, around 0.1 per cent, but when the edema is produced by capillary poisons, such as histamine, it is rich in protein (1.0 per cent). The application of these facts to the study of certain types of nephritis will be mentioned later.

The varying elasticity or resistance of the body tissues has a determining effect on the location and rate of edema formation. In chronic edema this tissue resistance may be decreased and hence edema is produced more easily.

Anoxemia probably contributes its share in the tendency to edema by its effect on the capillary wall. Although the dilatation that is part of this reaction would cause a drop in pressure, the dilated vessel would tend to become more permeable to protein. Indeed, rarely does a single mechanism of edema formation act without secondary effects which tend to set off one or more of the other basic factors. The result is a complicated interrelationship of forces with the development of several vicious cycles.

Renal function cannot be ignored in discussing the causes of edema since the removal of water by the kidney is one of its important contributions. It is quite possible to cause edema by forcing fluids on a patient anuric from mercurial poisoning or on an uremic patient whose kidneys are badly damaged by nephritis. In the latter instance there may remain an inadequate number of glomeruli to handle a large intake of water. It is possible that in acute nephritis renal ischemia may contribute to the tendency to edema.

The influence of various salts, particularly sodium chloride, on edema has been long known to students in this field. Due to easier analytic methods chlorine was at first thought to be not only more significant than sodium but a primary cause of edema. Years later, Blum's work made it evident that sodium was the essential element, in fact he proved that other chlorides such as calcium or ammonium chloride had an exactly opposite effect upon the edematous patient from sodium chloride,

causing diuresis instead of water retention Blum considered the influence of sodium on edema to be a specific ion effect

Loeb and I have conducted electrolyte balance studies which lead us to believe that no such specific effect exists Comparative observations of the effect of sodium upon a normal man on a salt poor diet and upon a nephrotic patient made it apparent that there was no qualitative difference between the results in the two individuals Both retained sodium and water, the nephrotic individual with his disturbed osmotic equilibrium, retained a great deal more, of course, but the general physiological effect of sodium on his total water balance demonstrated nothing that could be called a specific ion effect

If one assumes, and it is obviously true, that no extracellular fluids can exist in the body unless they contain a certain concentration of sodium, then no increase in these fluids can take place unless more sodium is available It is apparent, therefore, that restriction of the amount of sodium in the diet of an individual with a tendency to develop edema will be a limiting force on its accumulation Conversely, an excess of sodium will accelerate edema formation, when the basic equilibria are already altered in that direction The essential influence, then, of sodium and its salts is a nonspecific one No one can deny that there exist in the literature of this subject, many instances of salt effects that seem to fall outside this simple concept but they are merely evidences that the unexplored area is still large They do not preclude in any way, the conclusion that sodium restriction is a fundamental therapeutic measure wherever the general tendency to edema exists

We may now turn to a consideration of the various types of Bright's disease and analyze them for the mechanisms which I have outlined in the foregoing discussion The most difficult and unsatisfactory type is acute nephritis The sudden onset of this type of edema and its wide distribution have led many clinicians to suggest that capillary damage of some unknown origin must be the basic disturbance Although there is no histological support for this idea, there is other confirmatory evidence Most important is the high protein content of the edema fluid in acute nephritis as reported by various workers I stated a few moments ago, that the damaged capillary allows plasma protein to seep through its walls and that it was conceivable that the amount of protein in edema fluid may constitute a gross index of capillary damage Therefore, since the protein content of edema fluid is high in acute nephritis, it has been

assumed that the capillaries are in some way abnormal. This view, though widely held, has no direct therapeutic implication because the capillary poison has never been identified.

Another hypothesis concerning the edema of acute nephritis holds that there are profound changes in capillary blood pressure, i.e., the physical pressure. Direct measurements have given varying results and are most unsatisfactory because of the crudeness of the methods. It is true that the arterial pressure is often elevated and we have been interested at the Presbyterian Hospital to find the venous pressure, also, above normal on several occasions. Further study is indicated. It is possible that more frequent venous pressure observations might lead to a better understanding of this type of edema. Cardiac support would certainly have to be considered in the presence of a rising venous pressure, and one might be able to forestall the acute cardiac failure seen occasionally in this disease.

The brightest spot in this analysis of the causes of edema in Bright's disease is found when we turn to the nephrotic syndrome. Under this heading are included true or lipoid nephrosis, the nephrotic stage of chronic glomerular nephritis and amyloidosis of the kidney. The most obvious cause of the edema that is so characteristic of these diseases is a lowered plasma osmotic pressure due to a striking decrease in serum albumin. Although Richard Bright over 100 years ago pointed out that the plasma in nephritis is often poor in protein, it was Epstein in 1917 who first called attention to the clinical application of the Starling hypothesis. Epstein showed that a low serum protein implied a lowered osmotic pressure and that thereby the equilibrium between capillary blood pressure and plasma osmotic pressure was altered in a direction that would further the collection of fluid in the tissue spaces. It was subsequently proved that this decrease in serum protein is almost exclusively in the albumin fraction so that the normal albumin-globulin ratio is reversed. Since the albumin molecule is much smaller than the various globulin molecules, it exerts a proportionately higher osmotic pressure, consequently, its loss from the blood stream causes an even more serious diminution in plasma osmotic pressure than was suspected from the originally observed decrease in total protein. Further confirmation of this concept is found in the fact that only a small amount of protein appears in edema fluid from this group of cases, an observation which seems to indicate a relatively intact capillary wall.



There can be no doubt that lowered osmotic pressure plays an important role in the production of edema in the nephrotic individual. Omission, therefore, of careful determinations of this constituent from the clinical appraisal of such individuals with edema or indeed any patient with edema is excusable solely on the basis of total lack of laboratory facilities. We cannot by any known method stop the forces decreasing the serum albumin in these cases, hence, the rational therapeutic indication in the nephrotic type of edema is restoration of the osmotic pressure of the blood. No satisfactory method for doing this by increasing the plasma proteins is yet available. High protein diets have been disappointing as far as elevation of the serum protein levels is concerned, but it is obvious that the great loss of albumin in the urine requires a more than average protein intake. Certainly protein restriction is most unwise. In the usual case, 100 gms of protein a day will maintain a positive nitrogen balance. An effort to add to the protein content of the blood by transfusions is expensive and the benefits are not at all spectacular. It is not a therapy to be summarily discarded but it is usually rather disappointing.

Another rational method of raising the osmotic pressure would be the infusion into the blood stream of a substance whose molecules were so large that they could not pass through the capillary wall. They would thus exert osmotic pressure in the same fashion as do the plasma proteins themselves. Gum acacia is such a substance and its use does cause diuresis, although not in every instance. Recent work by Lepore seems to indicate that the chief effect of gum acacia is to increase the blood volume and this author believes that the diuresis follows an increased glomerular filtration derived therefrom. Lepore suggests the use of 500 cc of 6 per cent acacia in normal saline on three successive days. It is only fair to add that some workers report severe reactions to these acacia treatments.

As we turn from our discussion of the nephrotic type of edema, it is necessary to add that although a lowered osmotic pressure is the chief etiological mechanism and the only accurately measurable one, nevertheless, any clinician experienced in this field has seen instances of a wide discrepancy between the serum albumin levels and edema accumulation or diuresis. These situations remain unexplained.

Chronic glomerular nephritis often reaches the uremic or pre-uremic stage without edema formation, in fact dehydration is a more common complication in severe uremia. When it does appear, however, it may be the resultant of several mechanisms occurring separately or in various

combinations. It is rarely massive or extensive.

A decreased plasma osmotic pressure may occur in the uremic stage of chronic glomerular nephritis, and its degree of disturbance be appraised by a study of the serum proteins. A low serum albumin is occasionally the residue of a preceding nephrotic stage. On the other hand, it may be in part the result of malnutrition due to anorexia or vomiting. Rarely, however, does the fall in protein content from either cause reach levels at which edema formation is inevitable. Another common factor is circulatory failure. Cardiac hypertrophy and insufficiency often appear in the terminal stages of chronic nephritis. The consequent venous congestion raises the capillary blood pressure and edema results. Direct study of the venous pressure throws light on this type of pathological physiology. Digitalis and rest as in any cardiac insufficiency are indicated here. Severe anemia may complicate the uremic state and add its not too well comprehended effect, possibly anoxemic, in the direction of edema formation. Transfusion will help the anemia and also be of some benefit to the plasma protein levels. However, if cardiac failure exists, transfusions must, of course, be ordered with some caution.

It is apparent from the foregoing discussion that each type of Bright's disease must be carefully appraised in order to determine the mechanisms which are producing the edema existing in that particular case. The rational therapy applicable to each mechanism is derived from these physiological indications.

In addition to this specific therapy, there are a few general principles that obtain in the treatment of any form of edema. Foremost among these is sodium restriction. Even before edema accumulates in large enough quantities to cause any subjective reactions in the patient, it is advisable to institute a rigidly salt-poor regime. Practically, this means the preparation of all foods without salt and the avoidance of medications containing sodium chloride or bicarbonate. Not infrequently a patient on such a regime is discovered using a saline mouth wash or bicarbonate tablets for dyspepsia. The so-called salt substitutes are of little value as condiments and usually are sodium salts of some organic acid. Potassium chloride in a shaker has been recommended but most patients refuse it. Water restriction is of less value, but it is wise to keep total fluids down to 1500 cc. This is particularly true when cardiac insufficiency plays a role.

It is often necessary to stimulate the elimination of edema before the

underlying disease process has yielded to treatment or has run its natural course. Although there is rarely any place for this approach in acute nephritis, it is at times of real benefit in the nephrotic syndrome. This leads us to a discussion of the diuretics. It may be stated in general that when a diuretic is successful in producing a large flow of urine it is rarely harmful and it is equally true that continued administration without such effect is disturbing to the patient and indeed may be dangerous!

The most innocuous diuretics are found in the so-called saline group, consisting of calcium, ammonium and potassium chlorides or nitrites. They may react poorly upon the stomach and in the presence of severe renal insufficiency may produce rapid acidosis, but usually can be taken over long periods without trouble. This applies particularly to the calcium and ammonium salts. Unfortunately, they do not always stimulate urinary output. The usual dosage of ammonium or calcium chloride is 5 to 10 grams a day. Another harmless but less successful diuretic is urea. It is given in doses of 15 grams three times a day. Theocin and diuretin are examples of another group—they too are harmless but not very potent.

The mercurial diuretics such as salyrgan or mercupurin have the highest percentage of successful results, both as to the number of individuals responding and the amount of urine excreted following administration of the drug. Use of these drugs subsequent to a few days of ammonium chloride ingestion, produces a much larger diuresis than either the saline or the mercurial alone. The benefit of the salt usually appears after there is a moderate drop in the blood carbon dioxide, such as 5 to 10 vol per cent. A typical diuretic course of ammonium chloride and mercupurin consists of four days of daily 6 to 8 gm doses of ammonium chloride followed by 1 cc (or if glomerulonephritis exists only 0.5 cc) of mercupurin intravenously. If this is not successful the ammonium chloride should be continued and in two days 2 cc of mercupurin injected. If there is a striking diuresis one can continue the ammonium chloride indefinitely with mercupurin every five to seven days, until the edema has disappeared. If the first dose in glomerular nephritis is unsuccessful, the use of mercupurin should be discontinued. Urine examinations should be made every two or three days for the appearance of an increase in red blood cells. Mercupurin has been successfully used in the form of rectal suppositories. Although I have used mercurial diuretics without harm in true nephrosis, I have hesitated to give it in the nephrotic stage of chronic glomerular nephritis, where the kidneys are

presumably in a state of subacute inflammation. However, other workers have done so, particularly in children, with no apparent harm—although the estimation of such harm would be difficult unless it were very severe. I would advise strongly against the use of this type of diuretic in patients who show evidence of decreased renal function.

Sweating, purging and colon irrigations are therapeutic procedures of real detriment to the general condition of the patient and moreover are far afield from the basic problem. Hence we feel that they have no place in the treatment of Bright's disease in any of its various forms.

It is apparent as I conclude this discussion that there has developed in recent years a gratifying array of knowledge concerning the various types of Bright's disease. But it is also clear that there are many hazy areas and much more yet to be learned. We have just scratched the surface, indeed we have not even done that in the field of basic etiology. It is all the more necessary, therefore, to be meticulous and energetic students of such facts as are contemporarily available.

## MANAGEMENT OF TUMORS OF THE KIDNEY AND URETER\*

ARCHIE L. DEAN, JR

Associate Surgeon Memorial Hospital

THE purpose of this paper is to discuss briefly the natural history, clinical findings, and treatment of the three most common types of kidney tumors, namely, Wilms' embryonal adenosarcomas, tumors of the parenchyma in adults, and papillomas and epidermoid carcinomas of the pelvis and ureter. Probably the end results following the treatment of renal tumors have shown less improvement than has occurred in any other diseases of the genito-urinary organs. In spite of many brilliant advances in the practice of urology the fate of the patient with a kidney tumor today is little better than it was twenty years ago. These tumors are characterized by their "silent" development. The greater part of their life history can take place without the production of any symptoms. When they do arise, the symptoms may not appear urgent. Physical findings are rarely pathognomonic and if the majority of cardinal diagnostic signs are present the disease is usually far advanced and often uncontrollable with present methods.

The difficulties of the problem should stimulate physicians to greater alertness in discovering these tumors in earlier stages and applying the best treatment promptly. The laity should be taught the value of periodic physical examinations and the advisability of consulting their physicians without delay if symptoms occur.

Wilms' embryonal adenosarcomas are congenital mixed tumors of the kidney anlage. The average age when this tumor first appears is about three years, although it has been found in the seven months fetus and has affected adults. It is exceedingly rare after the age of seven years. Studies of the tumors of childhood show Wilms' tumors to be second in frequency only to tumors of the eye. Without doubt they are the most common tumors of the genito-urinary tract.

It is impossible to discuss the extensive literature concerning the

\* From the Department of Urology, the Memorial Hospital.  
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genesis of Wilms' tumors. It seems reasonable to suppose, however, that since these tumors may vary so markedly in the degree of differentiation of their component cells and in the number of tissues represented, they probably originate at different developmental periods of the embryo.

Wilms' tumors may be located in any part of the kidney parenchyma although the lower half of the organ seems to be involved most frequently in contrast to Grawitz tumors in the adult. The growth is always within the renal capsule unless the capsule has been ruptured. The encapsulation of Wilms' tumors has often been emphasized. It so completely separates the tumor from the renal parenchyma that the growth is described as being "in" the kidney but not "of" it. That portion of the kidney which is not destroyed may maintain its usual shape but it looks like a cap fitting on the tumor.

Wilms' tumors usually remain within the renal capsule until they reach a huge size. After the capsule is ruptured they grow aggressively by direct extension. From the retroperitoneal tissues adjacent to the kidney they spread to the omentum and nearby organs of the peritoneal cavity and may affect all the abdominal viscera. The walls of large blood vessels, especially veins, and the ureters have been destroyed. Even the diaphragm offers only slight obstruction.

The veins within the tumor are large and their walls are thin and fragile. Frequently they rupture spontaneously and often they are invaded by tumor cells. As a result, although extension does take place through lymphatics, the earliest demonstrable metastases are blood-borne and are found in the lungs and brain.

As the tumor grows in the infant there is a gradual distention of the abdomen accompanied by constipation and malaise. After a time, quite by accident in the majority of cases, a mass is discovered in one side of the abdomen. If growth is not stopped it is usually not long before there is a sudden augmentation of symptoms such as vomiting, loss of weight, asthenia, anorexia, increased rate of tumor growth, and the appearance of tortuous, dilated, superficial veins. It is of only academic interest that soon ascites is present, emaciation becomes marked, the abdomen enlarges tremendously, and probably metastases become obvious. Death follows from cachexia or intercurrent disease.

The first symptom in our twenty-four patients was

- 1) accidental discovery of a mass in the abdomen, 64 per cent
- 2) pain in the loin or abdomen

3) asthenia and malaise	12 per cent
4) hematuria	4 " "
5) frequency of urination	4 " "

Hematuria, usually unaccompanied by pain, is noted in between 10 and 25 per cent of children with Wilms' tumors. This is in contrast to the much greater incidence of 75 to 85 per cent found in adults with parenchymal tumors. The difference can largely be accounted for by the encapsulation of Wilms' tumors. Not infrequently the bleeding is from the congested parenchyma of the kidney rather than from the tumor proper. Hematuria is always intermittent and recurs at irregular intervals. The blood is diffused throughout all of the voided urine.

Pain is seldom an important symptom. It may be colicky, associated with constipation, or it may occur when the rapidly growing tumor exerts tension on the renal capsule or traction on adjacent organs. In babies this pain is difficult to evaluate.

Urinary signs are usually insignificant and unimportant. This again is probably due to the separation of the tumor by its capsule from the renal pelvis and parenchyma. Erythrocytes are sometimes found on microscopic examination but normal bladder urine may be found many times especially when the diseased kidney does not function because of pressure atrophy. Urinalysis may aid in detecting the onset of infection, and the appearance of albuminuria is noteworthy when it follows pressure on the tumor.

A palpable tumor is a most important observation in either a child or an adult, but in a child it may be the only diagnostic sign. There may be great difficulty in feeling the tumor if the child is obese. Also in young children the kidney normally lies deeper in the pelvis than in adults, sometimes extending as low as the crest of the ilium. Careful bimanual palpation of a Wilms' tumor may demonstrate its location, size, shape, consistence, mobility, and tenderness to pressure. The surface is usually smooth, although in later stages it may be lobulated. When necrosis occurs or hemorrhage takes place into its substance the tumor may feel as soft as in hydronephrosis. Mobility largely depends on the amount of available space remaining in the abdomen because primary tumors are seldom adherent and usually move with respiration.

Because the most careful general physical examination can not prove the presence of a Wilms' tumor and because at the time a suspicious mass is discovered the disease is far advanced, other diagnostic measures

must be carried out without delay. In most cases excretory pyelography will show what appears to be an enlarged kidney with characteristic pressure deformities of the pelvis and calyces. However, poor function or complete obliteration of the pelvis and calyces may render this test unsatisfactory. At this time, if not before, the patient should be referred to a urologist. It should be common medical knowledge, unfortunately it is not, that a complete cystoscopic examination with ureteral catheterization can be performed with little difficulty on the youngest infant of either sex. These procedures with retrograde pyelography should be sufficient to establish the diagnosis and determine the function of the opposite kidney. Under no circumstance should the tumor be incised to obtain material for a microscopic examination. This ill-chosen operation destroys the capsule of the tumor and permits more rapid and widespread growth.

Until recently surgery alone was employed in the treatment of Wilms' tumors and the results were bad. No figures are available, but it is questionable if 1 per cent of the patients survived five years. Principally because of their embryonal nature but also because they had other characteristics in common with tumors whose high radiosensitivity had been proved, radiation was first applied to Wilms' tumors about fifteen years ago. Although the patients were few and the disease in all was hopelessly advanced such marked regressions were observed that the recommendation was made that all Wilms' tumors which had not spread beyond the kidney should be irradiated and removed. If metastasis had occurred irradiation alone should be used. The recommendations concerning nephrectomy are now withdrawn. Personal experiences and those of others have shown that even after sufficient irradiation has been given to cause disappearance of the tumor and an apparently complete nephrectomy has been performed, local recurrences or metastases usually follow. Furthermore, microscopic examinations of the irradiated tumors showed a considerable amount of apparently unaffected tumor tissue remaining. It became evident that either not enough irradiation had been given or the tumors had been removed too soon for full irradiation effects to have become established. On the other hand if sufficient irradiation can be given to cause complete disappearance of the tumor and enough time elapses for cellular devitalization to take place, why operate? Therefore we now treat Wilms' tumors in whatever stage they may be with irradiation alone and the results so far are better.



The region to be treated extends from the anterior midline to the posterior midline of the body on the side containing the tumor. Four portals are outlined in this area. The width of each portal is one-fourth of the semicircumference of the infant's body over the tumor and the length of each is the distance from the upper to the lower ends of the tumor. In practice the portals are about ten by five centimeters in size. Using the 200 kilovolt Roentgen-ray unit at fifty centimeters' distance with one-half millimeter of copper and one millimeter of aluminum as filters 200 r may be given daily to a single portal.

In the majority of cases regression can be observed in a few days and it may be so rapid that a large tumor will disappear in two weeks. When the tumor has definitely become smaller the daily dose should be reduced to 100 r, an amount which can usually be well tolerated until treatment is completed. Since the minimum dose required to control these tumors is unknown, irradiation is continued to full skin tolerance. Using the portals in turn it is possible to give 3,000 r to each without producing more than an erythema in the skin. In a three year old infant of average size this treatment will deliver about seven threshold erythema doses to the region of the renal pedicle.

The greatest care must be observed when irradiating young children because they are relatively intolerant to the agent. The diet should be carefully chosen to maintain general health and blood of high quality. An examination should precede each daily treatment. Blood counts should be made at three-day intervals and roentgenograms of the chest should be taken every two weeks for the first few months. Excretory pyelograms made every two to three weeks will usually show the amount of tumor regression. Should the patient become anemic or the white blood cells fall below 2,000 per cubic millimeter, transfusions are indicated.

The writer realizes that it may seem quite radical to eliminate surgery completely in favor of irradiation in all cases of Wilms' tumors. However, no one can question the fact that the primary tumors markedly shrink under irradiation. For this reason and because radiation is now widely available the time has passed for any surgeon to attempt the removal of a growth weighing one-fourth or more of a child's entire body weight, nor is it necessary to use the more hazardous transperitoneal approach.

A preoperative cycle of irradiation can be given by using the same

factors described above except that the use of three portals rather than four saves time. No attempt is made to give a definite total quantity of radiation because nephrectomy is performed when the tumor has regressed to approximately the size of a normal kidney. In operating the greatest care must be taken to avoid rupturing the tumor capsule because if any of the growth spills into the wound prompt local recurrence is the rule.

Metastases should be irradiated with fractional doses applied through as many portals as the affected part of the body permits. Secondary deposits which can be discovered, such as those in the lungs, will often disappear under treatment, but in our experience the patients succumb to other metastases, usually in the brain, which were undetected until late symptoms such as convulsions or paralysis occurred.

No comprehensive study of the end results of radiation therapy in Wilms' tumors has been made because, to my knowledge only two primary operable patients have been treated with irradiation alone. Each is a healthy, growing child without demonstrable evidence of disease, one fourteen months and the other four years after treatment was started.

Between the ages of seven and forty years, kidney tumors are extremely rare. The great majority of adult tumors occur in patients between forty and sixty, with fifty-two years the average age of greatest frequency.

There are several histologically different tumors of the renal parenchyma in adults. At present their etiology is obscure. We will discuss only the most common, which are adenocarcinomas originating from the epithelium of renal tubules. Clear celled and granular celled varieties are commonly described but beyond the fact that clear celled tumors are more likely to be single, encapsulated, orange in color, and hemorrhagic, while granular celled tumors are more frequently multiple, non-encapsulated, white, more cellular and less vascular, the clinical differences are unimportant. The tumor begins in some portion of the parenchyma, either the cortex or the medulla, and grows by expansion and infiltration. It seems to be a characteristic of these tumors to grow toward the pelvis and penetrate it. When this occurs hematuria follows. From the pelvis the growth may steadily continue down the ureter for a considerable distance, but it does not give rise to secondary tumors in either the ureter or bladder. The renal capsule is a natural barrier, but the unchecked tumor is likely to destroy it after a time and extend widely in the perirenal

tissues While encapsulation of adult tumors is not unknown, it is rare compared with the regularity of encapsulation of Wilms' tumors Principally for this reason the symptoms of embryonal and adult tumors are different However in most cases no symptoms arise for a considerable time In these adult tumors the walls of the blood vessels are thin and friable They often rupture spontaneously with the production of hemorrhagic infarcts and areas of necrosis Tumor cells frequently perforate the delicate walls of the vessels and may break away and travel through veins to set up secondary deposits in the lungs, liver, brain, or bones Sometimes a solid extension of the tumor grows through the renal vein into the vena cava and even to the heart

The earliest symptoms are painless hematuria, pain in the kidney region, or discovery of a mass in the upper abdomen In most cases when the first symptom occurs the disease is well advanced Not infrequently a patient, unaware of any kidney trouble, seeks relief because of a metastasis Varicoceles occurring in middle age should arouse one's suspicion of a retroperitoneal growth which may press upon a spermatic vein or occlude the opening of the left spermatic vein by an intravenous extension

Painless hematuria is the initial symptom in about 70 per cent of all cases Bleeding occurs at some time in the course of about 90 per cent The blood, characteristic of all renal bleeding, is diffused throughout the entire specimen of urine If the hemorrhage is profuse, clots may form in the ureter or bladder and give rise to ureteral colic or dysuria Cylindrical blood casts of the ureter are of considerable diagnostic significance In all cases hematuria is intermittent and may not recur for months

While the sudden appearance of bloody urine is a severe shock to most persons, as soon as bleeding stops without other symptoms arising their equanimity is only too easily restored, especially when relief coincides with the administration of a urinary antiseptic and a physician's assurance that "a bit of gravel must have passed" It can not be too strongly emphasized that hematuria always indicates organic disease somewhere in the genito-urinary tract and no efforts should be spared to discover the place of its origin and the cause

Pain is much less frequent as an initial symptom, but in the majority of patients it occurs at some stage of the disease Pain in the kidney region is usually due to tension on the renal capsule It may come on suddenly with the occurrence of a hemorrhage into the tumor substance This type

of pain usually subsides. However, pain in the kidney region which steadily becomes more severe suggests extension of the disease beyond the capsule, perhaps with nerve involvement.

In most cases when hematuria or pain occur an enlarged kidney can be palpated, although if the tumor involves the upper pole this may be impossible.

A minority of perhaps 15 per cent of patients seek advice for progressive loss of weight and strength and a kidney tumor is discovered. In this group prognosis is especially bad because the tumor has perforated the renal capsule before growing into the pelvis and an extensive extra-renal growth has developed without giving rise to any localizing symptoms.

While a careful general physical examination is essential, a detailed study of the tumor can be made only by following urological methods. Whenever possible one should demonstrate the type of the tumor, the separate function of each kidney especially the sound one, whether or not the primary tumor has grown through the renal capsule, and the location and extent of possible metastases.

Excretory pyelography may furnish helpful information but in general the test has proved of less value than had been hoped. Cystoscopy with bilateral ureteral catheterization, dye elimination, urea clearance tests, and retrograde pyelography give the greatest information. In a few cases perirenal insufflation may show that the renal capsule has been ruptured. The function of the diseased kidney is a matter of great possible variation and of but slight importance. Whether or not the opposite kidney alone can maintain life must be known.

The interpretation of retrograde pyelograms is sometimes exceedingly difficult. The tumor may press on the pelvic region so firmly that no contrast medium can be seen or faint traces can be visualized only when the Roentgen rays strike the injected fluid tangentially. Greater difficulties are present when the changes are least marked. In general parenchymal tumors cause alterations in size and shape, often forcing the kidney out of its normal position and pressing on the pelvis and calyces to cause bizarre filling defects in certain calyces and elongation of others.

With radiation therapy emphasizing the importance of knowing the cellular composition of tumors before treatment is given, attempts have been made to obtain a preoperative diagnosis of the structure of renal tu-

mors Of course full advantage could be taken of this information only if successful specific therapy were available As yet neither diagnostic nor therapeutic measures are sufficiently refined However, within the past two or three years aspiration biopsies have been performed on kidney tumors The method, in general, is the same as for the aspiration of tumors in other locations, described by various workers in the Memorial Hospital With the patient lying prone with a pillow under the abdomen the tumor is located by its relation to bony landmarks in the roentgenogram compared with those on the body After suitable skin preparation and anesthetization a long eighteen-gauge needle is inserted until the external end moves with respiration This indicates that the point is in the kidney Negative pressure is exerted with a tightly fitting syringe while the kidney is probed The needle is then withdrawn and whatever tissue it contains is blown out on a glass slide, spread with another slide, fixed, and stained The entire process requires less than ten minutes Tissue should be easily obtained from every parenchymal tumor A competent pathologist, given tissue, can state with assurance whether or not tumor cells are present but he cannot, in all cases, determine the type of tumor The test helps little in predicting the tumor's radiosensitivity because that must be determined largely by trial and it is of no prognostic value since prognosis depends on factors other than structure

Nephrectomy is the only treatment which can control tumors of the renal parenchyma in adults The operation should be performed in all cases unless the patient's general condition is bad, the function of the opposite kidney is insufficient to maintain life, or the disease has spread beyond the kidney either by local extension through the capsule or by distant metastases

Study of the end results of the surgical management of tumors of the renal parenchyma in adults reported by a number of observers indicates that about 25 per cent are inoperable when first seen, the mortality of nephrectomy varies between 15 and 30 per cent, and about 15 per cent of the patients are well after five years

While the unqualified statement that radiation should play an important part in the management of all Wilms' tumors seems justified, the writer believes that as yet radiation has proved of slight clinical value in the treatment of renal adenocarcinomas This opinion unfortunately conflicts with a number of highly optimistic reports in the literature Under irradiation a large majority of these tumors shrink This regres-

sion in size has been the principal reason for the assertion that the tumors are radiosensitive. However, examinations made after nephrectomy show that the principal demonstrable change consists in injury to the thin walled blood vessels with the production of infarcts. While a considerable amount of tumor tissue is undoubtedly devitalized within the infarcts, yet apparently unchanged tumor cells can be found in immediately adjoining areas. Furthermore, it is difficult to determine how much value to attribute to irradiation because, as we have seen, infarcts occur spontaneously in these tumors and even with the microscope one cannot clearly differentiate spontaneous infarcts from those produced by irradiation.

The writer believes that the following conclusions represent a fair estimate of the proved value of radiation in the treatment of these adult tumors:

- 1 Radiation alone cannot control the tumors
- 2 Preoperative irradiation will diminish the size of the majority of the tumors. This may facilitate nephrectomy. The value of irradiation in these cases is approximately equal to partial removal of the tumor.
- 3 Irradiation will not make an inoperable tumor operable. A tumor is considered inoperable when it has perforated the renal capsule and invaded the perirenal tissues. Large size alone does not constitute inoperability because the surgeon's skill is an important factor.
- 4 If tumor cells are disseminated by the unavoidable trauma of a skilfully performed nephrectomy, and this has not been proved, a preoperative cycle of radiation probably cannot prevent the disaster.
- 5 During the course of a preoperative cycle of radiation and the period of waiting for its effects to become established and regeneration of the superficial tissues to take place, metastasis may occur.
- 6 If a tumor recurs locally, even though the recurrence appears superficial, external irradiation may diminish its rate of growth but will not stop it.
- 7 Metastases from renal adenocarcinomas show great differences in radiosensitivity depending on their location. Secondary deposits in the lungs frequently disappear while those in bones are inhibited slightly if at all.

The following factors have furnished satisfactory preoperative irradiation: the 200 kilovolt unit, filtration by two millimeters of copper, a target skin distance of seventy centimeters, and anterior, lateral and

posterior portals, each about fourteen by ten centimeters in size. A single portal is given 250 r daily until each has received 2,500 r. This treatment requires about a month and delivers to the region of the renal pedicle about five threshold erythema doses in a man of 150 pounds (68.2 kg) weight. After studying the radiation required to control other tumors, for there is no definite information regarding renal adenocarcinomas, it seems reasonable to believe that this amount is somewhat less than one-half of a curative dose. In most cases there is superficial blistering of the skin but healing is complete in about six weeks. At the end of this time, or two and one-half months after irradiation was started, nephrectomy can be performed with little if any noticeable delay in healing.

An inoperable kidney tumor should always be irradiated because nothing else is of the slightest help and the palliative effects of radiation are often considerable. In these cases maximal doses should be given and it is not as important to keep within a time limit or to preserve the skin so carefully. Four portals are used, each about fourteen by ten centimeters in size, the other factors remaining the same as in the preoperative cycle. With an additional portal greater skin regeneration takes place between treatments and it is often possible to give 3,000 r or even more to each portal. This furnishes about seven threshold erythema doses to the pedicle region of a man weighing about 150 pounds.

While these doses of radiation are well tolerated by most adults all patients should be carefully observed. The quality of the blood must be kept high because anemic individuals probably respond less favorably to irradiation. A diet rich in liver or liver extracts is helpful but transfusions of whole blood are best.

Papillomas and epidermoid carcinomas of the renal pelvis and ureter have the same structure and growth characteristics as epithelial tumors of the bladder. Little more is known about their etiology than that of the other kidney tumors. Chronic irritation by calculi seems to precede a definite number of epidermoid carcinomas and the changes between chronic productive inflammation through leucoplakia to clearly demonstrable cancers have been followed in several studies. Infection, always present with large calculi, may play some etiological part, but how much is uncertain. Other factors, still unknown, must be even more important because, while it is possible in a number of stone cases of long duration to find tumors in about 20 per cent, no antecedent history of stones can be obtained in between 75 and 90 per cent of tumors.

The papillomas, of a relatively low grade of malignancy, gradually spread from their usual place of origin in the pelvis down the ureter and into the bladder. Perhaps the condition is a disease of the mucous membrane of the entire urinary tract. At any rate it may become widespread and there is frequent recurrence on the opposite side. It has been suggested but not proved that the etiological factor is some carcinogenic substance eliminated through the kidneys.

The first symptom of papillomatosis is usually hematuria. This may not occur until the disease has spread as far as the bladder and the bladder tumors bleed. The hematuria is intermittent and usually painless. It is likely that erythrocytes are present in the urine for several months before frank bleeding occurs but they are rarely discovered because routine urinalyses are too seldom made.

Obstruction at the ureteropelvic junction and infection are regularly present even in early cases and either may cause vague sensations of discomfort in the kidney region or temperature elevations. There are no localizing symptoms in most cases, possibly because changes in the kidney are gradual and they are accompanied by progressive destruction of function.

Diagnosis is usually established by retrograde pyelograms although catheterization of an obstructed ureter is sometimes difficult. Excretory pyelograms are usually unsatisfactory owing to diminished function. Discovery of a papilloma in or near a ureteral orifice should always arouse suspicion concerning its possible origin higher up in the urinary tract. When pelvic and ureteral papillomatosis spreads to the bladder mucosa prognosis becomes more grave. Retrograde pyelograms show a striking picture of multiple filling defects in the kidney pelvis and ureteral lumen caused by the many papillary tufts. Usually the calyces are markedly dilated and the parenchyma is correspondingly reduced by pressure atrophy. As soon as this disease has been discovered one must learn not only the function of the opposite kidney but whether or not it is affected with similar growths.

The treatment in all cases should be nephro-ureterectomy. There is a good chance for success because the disease remains for a long time within the urinary tract. Radiation is not recommended because complete tumor regression would be most unlikely and there are no advantages in conservative measures because the function of the kidney has usually been lost.



A two stage operation is advisable for the majority of patients. At the first stage the kidney is removed with about two-thirds of the ureter. About two months later one should excise the ureteral stump with a cuff of the bladder surrounding the ureteral meatus. For the second operation a pararectus incision has been found more convenient than the usual midline approach.

After operation these patients should be carefully followed with cystoscopic examinations performed about every two months for several years. Small papillomas springing up in the bladder can be readily destroyed by fulguration, but if tumors develop in the remaining kidney or ureter no curative treatment is known.

Epidermoid carcinomas of the renal pelvis are fortunately rare. In common with other kidney tumors they usually grow "silently" for a considerable time. The great majority are highly malignant and metastasis through lymphatics has usually occurred before symptoms arise. Cures are exceptional.

The usual initial symptom is painless hematuria, but if the tumor arises close to the ureteropelvic junction vague symptoms of obstruction may occur sooner. While it is often impossible to make an accurate pre-operative diagnosis the retrograde pyelogram furnishes the greatest diagnostic aid. In the region of the pelvis there may be a partial filling defect which has strikingly well defined margins due to their dense induration. Simple nephrectomy is the treatment of choice.

Fewer than 100 cases of primary carcinoma of the ureter have been reported. The average age of the patients was about fifty-five years. Chronic irritation seems to play an important etiological role because a large proportion of the tumors have been associated with calculi, leukoplakia, or ureteritis cystica. The tumors are usually of the higher grades of malignancy and metastasize through lymphatics comparatively early. Painless hematuria may be the initial symptom but renal changes caused by obstruction and infection are usually so pronounced that pain in the kidney region accompanied by elevation of temperature may precede bleeding from the tumor. The importance of urological study is demonstrated in patients such as these who have a serious disease with relatively insignificant symptoms. The most careful general physical examination cannot discover the underlying pathology in these cases but a pyelo-ureterogram will quickly solve the problem. As soon as the diagnosis has been made nephro-ureterectomy should be performed. At the same

time the lymphatics in the perirenal and periureteral fat should be removed. Postoperative irradiation is advisable in all cases of epidermoid carcinoma of the renal pelvis or ureter although its value is as yet uncertain.

### CONCLUSIONS

1 The "silent" development of renal tumors is largely responsible for poor end-results of their treatment.

2 In recognition of the difficulties of the problem the importance of periodic physical examinations should be stressed.

3 A mass in the kidney region of a child or sudden painless hematuria in an adult is the most frequent initial symptom of a renal tumor.

4 Aspiration biopsies can be safely performed on the kidney but the pathologist should interpret the microscopic picture with full knowledge of the limitations of the method.

5 A kidney tumor in a child should never be incised to obtain histological material.

6 No infant of either sex is too young for a complete urological examination.

7 Wilms' tumors are best treated with radiation alone. All other operable tumors of the kidney or ureter should be managed surgically.

8 The principal effect of irradiation on renal adenocarcinomas seems to be destruction of the delicate walls of blood vessels with the production of hemorrhagic infarcts. Although there is frequently complete destruction of tumor tissue within the infarcted areas one can usually find apparently unchanged cancer cells nearby. The clinical effect of preoperative irradiation in these cases is equivalent to partial removal of the tumor.

9 Since it is unlikely that the results of surgery alone will be materially altered, future improvement in the management of renal tumors will probably follow earlier diagnosis, advances in the use of the physical agents and discovery of other, better, methods of treatment.

## THE SIGNIFICANCE OF THE NEW YORK ACADEMY OF MEDICINE\*

### *Presidential Address*

JAMES ALEXANDER MILLER

WE HAVE this evening had the privilege of hearing from Doctor Krech a report of the activities of the Committee on Fund-Raising, of which he is chairman. The object of this Committee is to inform the citizens of New York City of the work of the Academy and of its services to the medical profession and to the community as a whole.

The Committee has published a very interesting booklet which contains much information with which probably many even of our own Fellows are unfamiliar and which will repay a careful perusal by all interested in the maintenance of high medical standards and the promotion of better health in New York.

While it is a primary object as well as a hope that this wider dissemination of knowledge concerning the Academy will aid in securing for it a broader base of financial support, at the same time this effort is largely an educational undertaking directed toward a better understanding of the activities and purposes of an important quasi-public institution all too little known to New York and to New Yorkers.

As it is the privilege as well as the duty of the President to address the Academy upon this occasion on some subject of general interest it appears timely to raise the question: What is the real significance of the Academy of Medicine?

Inasmuch as the material for this address is drawn largely from the same sources, it is inevitable that my discussion of this question will parallel in many respects the contents of the descriptive booklet to which allusion has already been made. However, as the approach is from a somewhat different angle, it is hoped that the repetitions which may occur may only add emphasis to important phases of the general subject, and that, in addition, sidelights of interest and value may be afforded.

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\* Delivered at the Annual Meeting January 6, 1938.

This pamphlet describing the Academy's activities presents the facts *objectively*. In it will be found in concise and concrete form a summary of what the Academy is doing. It is my purpose to deal with these same facts *subjectively*, that is, in terms of personal reaction to them. In other words, to raise the question as to what is, or may be, the significance of these Academy activities to various groups who are, or, we believe, should be, interested in them. The facts, being objective, may speak for themselves, but, if they are to have influence, they must be understood and interpreted in the consciousness and experience of those to whom they are presented. This is the subjective side of the situation. What is the significance of these facts, their meaning?

For our purpose the numerous individuals whom we wish to enlighten concerning the Academy may be divided into various groups

- I The members and Fellows of the Academy
- II Other members of the medical profession
- III The patients of these physicians
- IV The Institutions in the city, both public and private, which are organized for the treatment and prevention of disease
- V The general Community

### *I The Members and Fellows of the Academy*

In our effort to interpret the significance of the Academy it appears proper and logical that we begin with that group of us who are members or Fellows of this institution, for, after all, this Academy in some sense belongs to us, or at least the responsibility for its activities is primarily upon our shoulders.

So this evening first of all I am putting to you, the members of the Academy, the searching personal question. What does the Academy mean to you? It may be that you have never posed this question to yourself. If so, will you allow me for a few moments to try to give direction to your thinking?

There are 1700 active resident members and Fellows of the Academy from a total of over 14,000 physicians in the entire city. Why are we among this selected group? If you think that it occurs as a matter of course I wish that you might all know something of the careful deliberations of the Committee on Admissions. You would then recognize that each one of you has been selected because of certain definite attainments in your profession, and perhaps even more because of the promise which

was considered to be in you that you would go on to a greater fulfilment of your possibilities. On that account you were deemed worthy of admission to the privileges which the Academy offers to help you to make that promise good.

Is this an honor? In one sense yes, reflecting as it does the judgment of your own peers. But, is it not still more a responsibility? If so, how far have we lived up to this responsibility?

Look back over the ninety years of the history of this Academy! It is a story of the struggle of eager minds to crystallize the ideals of our profession into an institution which would be a vital instrument for furthering the ideals of a progressive betterment of the profession and of the health of the community. By slow and painful steps a library was gradually accumulated, there was provided a forum for the discussion of medical subjects, a medium for continued medical education, and an opportunity for leadership in the health problems of the city. Now, these things did not happen of themselves, nor were they the spontaneous gifts of an admiring and appreciating public—far from it. They were the result of persistent and strenuous labor on the part of physicians who believed in the Academy and were willing to work, work hard for it. And so finally at last we, as an Academy, have arrived at our present exalted station, ensconced in a setting of beauty, comfort and dignity, endowed with a Library second to none, with an equipment for study and discussion undreamed of by our predecessors, and a staff ready to render every service for which our forbears longed in vain so many years.

Now, do we, the present members, own this great thing which has been set up, have we proprietary rights in it? Are we not rather the temporary legatees of an institution handed down to us by our fathers and by those generous benefactors who were willing to support their ideals? We are but trustees for the nonce, obligated to carry on and in our turn to pass the Academy over to our successors, intact and enhanced in value because of our efforts.

Owners? Why, we do not even pay the carrying charges, to say nothing of the capital invested! We pay our dues, to be sure, but do you realize that their total amount is less than thirty per cent of our annual budget, that we do not even pay for the annual cost of the upkeep of our Library alone?

Our ownership is in a responsibility, not in tangible rights or privileges, and our membership is an obligation, a debt rather than a

recoverable asset

How can we repay this debt? I would suggest to you that if the Academy means what I would like to think that it does to us, we may do so in at least one of three ways

- 1) Payment by better utilization of our privileges
- 2) Payment in services
- 3) Payment in direct or indirect financial contributions

I would further suggest that you try not one, but all of these methods of payment. Let us consider each one in brief detail

1) *Payment by Better Utilization of our Privileges*—Our first thought here turns to the Library. We all know what a superb instrument for medical education it is. The books, the periodicals, the reference and bibliographical services combine to make its use easy, profitable and pleasant. In it, as members, we have certain minor privileges over the general public, such as a private members' reading room, the opportunity for evening use, and the privilege of withdrawing books.

Last year the Library had over 61,000 readers, of which 8000 were members of the Academy. Does this indicate that we are appreciating and utilizing our opportunities here as we should? Can we not make this wonderful Library mean more to us?

Then there are our meetings for medical discussions and exchange of ideas. Last year there were held seventy-seven meetings of our various eleven Sections, with a total attendance of 11,700, an average of 152 at each meeting—a very creditable evidence that these meetings certainly mean something to our members. The attendance at the Friday afternoon lectures and those held in connection with the Graduate Fortnight is very large. Although the physicians in attendance are predominantly non-members, it is obvious that these meetings are recognized as of real educational value.

The attendance at the regular stated meetings of the Academy is, on the contrary, often disappointing, in spite of the devoted efforts of the Program Committee to make them attractive. Perhaps one reason may be that they are conducted as didactic lectures without opportunity for discussion. Some of our Fellows have suggested this, but it is significant that similar lectures held on Friday afternoon are well attended. Perhaps it might be better if we held our stated meetings in the afternoon instead of in the evening.

This problem of the stated meetings has perplexed the officers of the

Academy for several years. They would welcome suggestions from the membership as to how these meetings can be made to have more value and meaning to the Academy.

In general it may be said that all of these opportunities above outlined are designed for the postgraduate education of physicians. This is the main function of the Academy, and if we all might appreciate and utilize them more, the Academy would certainly mean more to us.

2) *Payment in Services*—Here is a real opportunity to show what the Academy means to us.

In this connection I wish first of all to stress the work of our Academy committees. More than 200 of our members are each year serving upon one or more of our important committees. We are very proud of this work, and it is a valiant service indeed.

I wish that there were time to expatiate fully upon the amount and character of this committee work. It is second only in importance to our educational activities. Hours of devoted and hard labor is spent by these committees and their numerous subcommittees. This has meant much to the Academy, to the profession and to the community.

These committees help to operate the Academy, they study how to keep up our standards of service and of ethics, they work hard in the interests of the Library, they scrutinize with the greatest care the qualifications for admission to the membership, they plan the programs and study and provide for the varying educational needs, they are intimately concerned with numerous problems of public health and meet the demands for counsel and advice which come to them in ever increasing numbers from all sorts of public and private organizations as well as individuals. In this field of public health service alone the Academy has come to have a commanding position of influence in the community.

Another committee serves our publicity relations, assisting and advising the press in medical matters, giving reliable information to physicians and other citizens, protecting physicians from awkward publicity predicaments and restraining the activities of others to whom publicity is not awkward. This phase of our committee work has been reviewed with great care by the Council during the past year, and while it would appear that some modification of the program is desirable, it is also equally plain that the judgment of our first director, Doctor Linsly R. Williams was sound and that the Academy cannot shirk the assumption of some responsibility in this field of effort.

The work of our committees in general is magnificent, but only a little more than one-eighth of our total membership shares in it each year. It is our policy to make annual substantial changes in personnel, so as to distribute more widely the opportunity as well as the labor among our membership. Every member should be eager and ready to serve in some capacity for which he may be particularly fitted, and it is hoped that the opportunity may be available for many more members than at present.

A few years ago one of our Fellows, who later was elected to one of the highest offices in the gift of the medical profession and who had at that time served for several years our Committee on Public Health Relations, said in conversation: "Those meetings of the Public Health Committee have meant more to me in widening my horizon and teaching me the responsibility of medicine than anything that I have experienced since leaving the medical school."

This is what that particular committee meant to that man. It means that to many others, and in some form of service it could mean that to each one of you.

3) *Payment through Financial Contributions*—Now you will perhaps say to yourself that this is what the President has been leading up to, which is not true, although perhaps there may be some truth in it.

The plant and equipment of the Academy is worth conservatively \$2,600,000. We have an invested capital worth even at present prices \$2,700,000. The income from these investments is at present \$158,000 a year. In the main, it is this income which supports the Academy. While this seems like a good deal of money, yet even with careful management and economy it is not sufficient to meet our expenditures without a deficit unless there are additional contributions to our annual income. In addition, we are confronted with pressing needs which can only be met by still larger funds. The details of these needs have already been explained to you. Now what, if anything, are you, the members, intending to do about this? A few months ago we received, in response to a letter which was sent to all members of the Academy, a communication from one of our most valuable members from which I would like to quote:

He said: "I feel very strongly that the Academy is an asset to every one of its Fellows and members. I believe that every one should contribute something toward its deficit, and I am not willing to appeal to any of my well-to-do friends until I am assured that all of the members



of the Academy have subscribed to this fund For, if the Members and Fellows cannot individually subscribe at least one dollar a year, then I have not the effrontery to approach any of my lay friends "

Now, I have no intention of pressing this particular point But it is an index of what the Academy means to this particular Fellow, and it is perhaps significant that a favorable response to this preliminary appeal sent out last June was received from 258 members and Fellows, which number very closely corresponds in number as well as in personnel to those individual members who have served upon our Committees The active workers were the ones most ready to give, the Academy meant more to them Truly, appreciation best comes through service

When each one of you comes to think over the Academy in the light of the information which is being put before you as well as in the light of your own experience, will you not ask yourselves the question Is the Academy worth to me more than forty dollars a year?

I have purposely placed a good deal of stress upon the significance of the Academy to its own members, for it is upon them that the responsibility primarily rests

We will now proceed to examine the situation as it affects other groups in our community This may be done in a less exhaustive manner, as much of the material presented will be the same although the application and emphasis will be somewhat different

## *II The Other Members of the Medical Profession*

As has already been indicated, there are over 14,000 physicians in this city, of whom only 1700 are active members of the Academy It is obvious that an institution which pretends to provide opportunities for postgraduate education must offer them freely to all who are qualified as physicians to make use of them This the Academy does

The Library, the section and stated meetings, the Friday afternoon lectures and the Graduate Fortnight are all open to any physician With certain minor restrictions they have the same advantages in the use of these activities that are offered to our own members We also send free to every physician in the city our publication "Preventive Medicine "

That these opportunities mean much to these physicians is evidenced by the very considerable numbers which avail themselves of them There is no doubt that the Academy is regarded as the medical center for all physicians of the city, whether members or not, that it enhances mate-

rially the standards of medical practice and thus materially affects the welfare of the community

Consciously or unconsciously these outside physicians respect the standards of practice and of ethics for which the Academy stands, and a considerable number of them aspire to eventually being able to join our membership and thus secure the stamp of approval upon their proficiency which such membership would signify to them and to their colleagues

As our waiting list of applicants for admission grows, and when it becomes obvious that the present limitation of numbers is withholding the privileges of membership from a considerable number of physicians who desire them and are properly qualified, there is little doubt that the Council will decide to increase the membership to meet such legitimate demand. This has been done in the past and can quite well be done again in the future

In the meantime the Academy will continue to welcome within its doors all serious students of medicine and to render them assistance in their efforts to improve the quality of their work and also to provide for them a standard to which they may aspire

Thus the Academy has a real significance to the entire local medical profession, which is limited only by the capacity of each and every physician to appreciate it

### *III The Patients of these Physicians*

This applies to all physicians, whether members of the Academy or not, and to all patients under their care, whether in hospitals and dispensaries or in private practice

The main function of the Academy being to help develop better doctors, any progress which is made toward that end becomes immediately a service to the patients under the care of these doctors

Unfortunately, many patients still choose their medical advisors with less thought and care than they pay to their stock transactions or even to the selection of their tailors or dressmakers. In hospitals and dispensaries they usually have no opportunity for choice at all, but here they are protected by the wisdom and responsibility of various appointing boards who make the selection for them

Among the private-patient group, however, there is a gradually increasing appreciation of the fact that one's physician may be vitally important in one's life and that proper education and training means

more in a crisis than does an affable bedside manner

Many people, however, do not realize that the education of the physician is a continuous process through his entire professional life, and that when he ceases to be a student he at that selfsame moment begins to deteriorate professionally and finally to dry up and wither away

There can be no question that the chief element in this education is experience, properly utilized and interpreted. The most valuable source of this experience comes from the hospitals with their large clinical material and their opportunities for the close study and observation of many cases of disease. With due regard to the tremendous value of the free service thus rendered by physicians in hospitals and dispensaries, I venture to think that the dominating motive which attracts every wide-awake physician to these hospital positions is not primarily humanitarian. That phase of our work we in general assume automatically to be the natural responsibility of our particular profession. Rather it is an irresistible impulse which drives such a physician constantly to strive to improve his medical knowledge and skill.

Granting the predominance of clinical experience in the attainment of graduate medical education, the next most important element is the opportunity for reading and the study of the current literature, so absolutely essential in these days of rapid growth in modern medical knowledge, and also closely connected with this is the opportunity for discussion and the matching of ideas and exchange of opinions with one's colleagues. It is in these phases of medical education that the Academy supplements practical clinical experience, and, as we have above shown, it does it in a very efficient way.

Thus, to all patients, rich and poor alike, the Academy, whether they know it or not, means that they obtain better medical services from the physicians who will avail themselves of these privileges, and that in the last analysis our patients are the ones who are the greatest gainers from the education which the Academy affords.

#### *IV The Institutions in the City, both Public and Private, which are Organized for the Treatment and Prevention of Disease*

By these are meant especially the hospitals and dispensaries with their allied services, on the one hand, and the organizations designed to render preventive services to the public, on the other. In addition, there are certain other public and private organizations not primarily concerned

with health or disease, among whose activities, however, certain health problems necessarily arise from time to time

The services rendered by the Academy in this category are largely through the activities of its Committee on Public Health Relations. We have already presented a general review of this service. It is difficult to overemphasize the dependence that certain public departments of the city government have come to have upon the advice and assistance of the Public Health Committee. This is especially true of the Health Department, of the Departments of Hospitals and Education, and also of the Civil Service Department. For example, during the past year this Committee has made a comprehensive report upon the organization necessary for determining the early type-diagnosis and the effective serum treatment of pneumonia. Also it has made, in cooperation with the New York Tuberculosis and Health Association, a study of the tuberculosis hospital situation. It has prepared regulations for the examination of medical inspectors in the Department of Education. Many detailed studies conducted at the request of the Department of Health or of Hospitals have been made and, in addition, specific recommendations concerning the items to be contained in the annual budgets of these departments. It has cooperated with the County Medical Society in a study of the possibility of requiring health certification for domestic servants and in cooperation with the New York Tuberculosis and Health Association a study has been made of the situation regarding tuberculosis as a compensable disease, especially with reference to nurses.

In cooperation with the Medical Information Bureau and the Committee on Medical Education, and upon the request of the Department of Education, there have been formulated plans for a series of lectures for school teachers on matters of health and hygiene, which would help them in the performance of their duties. It has also given assistance to the Civil Service Department in the formulation of examination requirements as well as the securing of competent personnel to conduct such examinations as they apply to medical positions in the various city departments.

These and many other services have been rendered and many reports have been prepared in various phases of the health problems of the city.

The testimony which has been freely offered to us from many sources and the increasing demand which comes to us for such services, are conclusive evidences of the significance of these activities to many important groups in the city, and it is hardly an overstatement to say that the gradual

development of the work of this Public Health Committee for more than twenty-five years is one of the outstanding achievements of the Academy

### *V The General Community*

In and through our entire discussion has run the suggestion that the Academy has a real significance to the community as a whole

The diffusion of medical knowledge throughout our membership and throughout the entire body of New York physicians, the advantages which thus accrue to thousands of suffering patients by assuring them of better treatment, the services of the Committee on Public Health Relations and the Medical Information Bureau to so many various groups in the population, and finally the general influence of the Academy upon the development of the better practice of remedial and preventive medicine, are all directly of great advantage to the public at large

It has been suggested by some intelligent but, I believe, ill-informed Fellows that the Academy would do well to confine its activities to strictly medical matters, mainly, if not exclusively, affecting our own membership. It has even been suggested that it would have more dignity and influence if it were possible to restrict these privileges to a much smaller number, perhaps not exceeding five or six hundred Fellows

Now, I can conceive of the attraction and charm that such a medical Athenaeum Club might have for the elect, but would it meet our responsibilities?

There is another very practical side to this question. During the past year we have been required by the Department of Internal Revenue to show cause why we, as a limited-membership corporation, should be exempt from taxes. A very searching investigation was made which required many months of serious preparation and anxious thought on the part of our Director and of our legal counsel who faced the possibility of our liability to real estate, to capital gains and to income taxes. The result was a complete victory for the Academy, but this was due solely to the substantiated fact that the Academy is rendering an outstanding public service entirely outside of, and outweighing any advantages to, its own members. We cannot afford to lose sight of this situation as we formulate our future program.

But apart from this very important practical consideration there are other compelling reasons of a more strictly medical nature. From the welter of acrimonious discussion concerning medical organization that

has gone on both within and without the profession during the past few years at least one significant fact emerges and that is that the medical profession cannot live to itself alone

While we quite properly claim the post of leadership in any projected changes, we cannot deny that the community as a whole has also a vital interest in this question. This problem has comparatively little to do with the curative side of medicine, nor, as it seems to me, are the economic factors as predominantly important as they have been made to appear. It is rather the social and preventive aspects of medicine which demand the close cooperation of the profession and of the laity alike. We physicians have been criticized, perhaps with some justice, for having neglected these fields which are now recognized to have become increasingly important. We have been deeply engrossed in our own essential job of trying to take good care of sick people, and it is quite possible that our preoccupation has too closely narrowed our vision of our other responsibilities. But in every field of medicine, whether curative or preventive, it is the quality of service which counts and no change of organization can supply this, for it must come from the better training and education of physicians. The Academy, as already described, has made significant contributions toward this end, and particularly has it served as a center through which has been focused the greater attention of the profession upon this social and preventive side of medicine. In this way we serve physicians and laity alike, and it does not appear thinkable that we can in any way curtail these services, rather it would appear that we must continually extend them. This, in addition to the development of our proficiency in curative medicine, is the basis upon which we have the right to state to the public that we are acting in their interest and thus deserve from them both interest and support.

So, as we now at this time go out before the public with our appeal, let us be sure that our own house is in order, that we, as individual members of the Academy, recognize and appreciate the true significance of the Academy and that this involves not only improving ourselves but also continually serving the community.

As we thus develop our interest in the collateral branches of social and preventive medicine for which the Academy stands, we will be surprised to find how much our own horizon has become widened and that we have unconsciously developed our own capacities as individuals, as citizens and as physicians.

# RECENT ACCESSIONS TO THE LIBRARY

"Possession does not imply approval"

- Aaron, R I *John Locke*  
London, Oxford Univ Press, 1937, 328 p
- Bleuler, P E *Lehrbuch der Psychiatrie*  
6 Aufl  
Berlin, Springer, 1937, 496 p
- Buie, L A *Practical proctology*  
Phil, Saunders, 1937, 512 p
- Carlson, A J & Johnson, V E *The machinery of the body*  
Chic, Univ of Chic Press, [1937], 580 p
- Davis, A H *Noise*  
London, Watts, [1937], 148 p
- Deirborn, F M *The Metropolitan Hospital a chronicle of sixty-two years*  
N Y, [privately printed], 1937, 351 p
- Doe, J *A bibliography of the works of Ambrose Pare*  
Chic, Univ of Chic Press, 1937, 266 p
- von Domarus, A *Grundriss der inneren Medizin* 11 Aufl  
Berlin, Springer, 1937 685 p
- East, C F I *Failure of the heart and circulation*  
London, Bale, 1937, 130 p
- Eppinger, H *Die Leberkrankheiten*  
Wien, Springer, 1937, 801 p
- Essig, N S *Prosthetic dentistry*  
Brooklyn, Dental Items of Interest Pub Co., 1937, 181 p
- Findlay, A *A hundred years of chemistry*  
London, Duckworth 1937, 352 p
- Fleischmann W *Vergleichende Physiologie der inneren Sekretion*  
Wien, Perles, 1937 147 p
- Gask, G E & Ross, J P *The surgery of the sympathetic nervous system* 2 ed  
London Bailliere 1937, 191 p
- Goring, M H *Über seelisch bedingte echte Organerkrankungen*  
Stuttgart, Hippokrates-Verlag, [1937], 82 p
- Guest I H *If air raid comes a guide to air raid precautions and anti-gas treatment*  
London Fire, 1937 88 p
- Hys, H M *Personality and other things (A semi-autobiography)*  
N Y, American Physician, [1937], 163 p
- Heidenham, M *Synthetische Morphologie der Niere des Menschen*  
Leiden, Brill, 1937, 270 p
- van der Hoop, J H *Bewusstseinstufen und ihre Beziehung zur Psychopathologie*  
Bern, Huber, [1937], 375 p
- International (1) Conference on Fever Therapy New York 1937 Fever therapy abstracts and discussions of papers*  
N Y, Hoeber, 1937, 486 p
- Interurban Clinical Club *History of the Interurban Clinical Club, 1905-1937*  
Chic, Winston, [1937], 279 p
- Ischlondsky, N E *Protoformotherapy in treatment and prevention*  
London, Kimpton, 1937, 237 p
- Joint Standing Committee on Library Co-operation, London *Union catalogue of the periodical publications in the university libraries of the British Isles*  
London, Joint Standing Comm on Library Co-op, 1937, 712 p
- Jouveux C F & Sicé A *Précis de medecine coloniale* 2 ed  
Paris, Masson, 1937, 1250 p
- Kenny, E *Infantile paralysis and cerebral diplegia*  
Sydney, Angus 1937, 125 p
- Kirk, J B *A manual of practical tropical sanitation*  
London, Bailliere 1937 300 p
- Klimpan H C *Lanthier du rein*  
Ivon, [Irevoux Patissier, pr], 1937, 190 p
- Klebs, A C *Incunabula scientifica et medica Short title list*  
Bruges Saint Catherine Press, 1937, 359 p
- Korner, O *Lehrbuch der Ohren- Nasen- Rachen- und Kehlkopf-Krankheiten* 13 Aufl  
Munchen Bergmann, 1937 342 p

- Kuczynski, M H *The alimentary factor in disease*  
The Hague, Nijhoff, 1937, 130 p
- Kurtz, C M *Orthodontic copy*  
N Y, Macmillan, 1937, 247 p
- Lang, F *Die Simulation in der Unfallmedizin*  
Bern Huber, [1937], 83 p
- Lawrence, R D *The diabetic life, its control by diet and insulin* 10 ed  
London, Churchill, 1937, 246 p
- L League of Nations Health Committee *Inter-governmental conference of Far-Eastern countries on rural hygiene Preparatory papers*  
Geneva, 1937, 2 v
- L League of Nations Health Committee *Report of the Inter-governmental conference of Far-Eastern countries on rural hygiene held at Batavia (Java), Aug 3rd to 13th, 1937*  
Geneva, 1937, 119 p
- Leveuf, J B *Études sur le spina bifida*  
Paris, Masson, 1937, 329 p
- Lewis, (Sir) I *Diseases of the heart* 2 ed  
London, Macmillan, 1937, 297 p
- Loewy, A & Wittkower, E *The pathology of high altitude climate*  
London Milford 1937, 212 p
- McBride, W C *Juvenile dentistry* 2 ed  
Phil, Lea, 1937, 391 p
- Malloch, A *Short years the life and letters of John Bruce MacCallum, M D*  
Chic, Normandie House, 1938 [1937], 343 p
- Mix, C H *Manual of the diseases of the eye* 15 ed  
Balt, Wood, 1937, 498 p
- Mayerhofer, B *Kurzes Wörterbuch zur Geschichte der Medizin*  
Jena, Fischer, 1937, 224 p
- Metropolitan Life Insurance Company *Twenty-five years of health progress*  
N Y, Metropolitan Life Ins Co, 1937, 611 p
- Mirall, S & Mirall, I M *Chemistry matter and life*  
London, Arnold, [1937], 295 p
- Mohler, H *Losungsspiel tren*  
Jena, Fischer, 1937, 92 p
- Moorhead, J J *Harlow Brooks, man and doctor*  
N Y, Harper, 1937, 302 p
- Mum, W *An eight-hundred year old book of Indian medicine and formulas Translated by F Shirpe*  
London Luzac 1937, 195 p
- Nay, W S *The old country doctor, an autobiography*  
Rutland, Vt, Tuttle, [1937], 87 p
- Nicholls, T B *Organization, strategy and tactics of the Army medical services in war*  
London, Bailliere, 1937, 372 p
- Nissen, R *Chirurgische Indikationen*  
Leiden, Sijthoff, 1937, 177 p
- Okinczyc, J *Humanisme et médecine*  
Paris, Labergerie, [1937], 140 p
- Papyrus (The) *Ebers, the greatest Egyptian medical document, translated by B Ebbell*  
Copenhagen, Levin, 1937, 135 p
- Pizzini, A *Isanti nella storia della medicina*  
Roma, Casa ed "Mediterranea", 1937, 605 p
- Rehberger, G E *Lippincott's quick reference book for medicine and surgery* 10 ed  
Phil, Lippincott, [1937], 1354 p
- Roxburgh, A C *Common skin diseases* 4 ed  
London, Lewis, 1937, 401 p
- Sadler, W S *Psychiatric nursing*  
St Louis, Mosby, 1937, 433 p
- Schinz, H R & Zuppinger, A *Siebzehn Jahre Strahlentherapie der Krebse*  
Eipzig, Thieme, 1937, 340 p
- Scritti di chirurgia ermaria per commemorare il cinquantenario della operazione di Bassini  
[Padova], Tip del Seminario di Padova, 1937, 2 v
- Simkins, C S *History of the human teeth*  
Phil, Blackiston, [1937], 329 p
- Smith, N R *Elements of orthopaedic surgery*  
Bristol, Wright, 1937, 246 p
- Whitby, I F H & Britton, C J C *Disorders of the blood* 2 ed  
London, Churchill, 1937, 582 p
- Wilder, R M *A primer for diabetic patients* 6 ed  
Phil, Saunders, 1937, 191 p
- Wilson, D W *A laboratory manual of physiological chemistry* 3 ed  
Balt, Williams, 1937, 288 p
- Winter, I *A textbook of exodontia* 3 ed  
St Louis, Mosby, 1937, 502 p
- Zeiss, H & Rodenwaldt, E R K *Einführung in die Hygiene und Seuchenlehre* 2 Aufl  
Stuttgart, Enke 1937, 282 p



## PROCEEDINGS OF ACADEMY MEETINGS

## STATED MEETINGS

FEBRUARY 3—*The New York Academy of Medicine* Executive session, Reading of the minutes ¶ Paper of the evening—The conception of cancer before and after Johannes Muller, Howard W Haggard, Associate Professor of Applied Physiology, Sheffield Scientific School, Yale University ¶ Report on election of members

FEBRUARY 17—*The Harvey Society in affiliation with The New York Academy of Medicine* Fifth Lecture, "Studies on the Cortical Representation of Somatic Sensibility," Philip Bard, Professor of Physiology, The Johns Hopkins School of Medicine

## SECTION MEETINGS

FEBRUARY 1—*Dermatology and Syphilology* Reading of the minutes ¶ Presentation of cases—a] Mt Sinai Hospital, 2] Miscellaneous cases ¶ Discussion of selected cases ¶ Executive session

FEBRUARY 4—*Surgery* Reading of the minutes ¶ Presentation of cases—a] Two cases of micro-aerophilic hemolytic streptococcus (shown as a group), John V Bohrer, Discussion by Frank L Meleney, b] Two cases of Wescott Nail for intracapsular fracture of neck of femur (shown as a group), Edward R Easton, Discussion by Clay Ray Murray, c] Incidental findings in gall bladder surgery, Pro V Prewitt, Discussion by Henry Horn (by invitation), d] Penetrating ulcer of the stomach, C Joseph Delaney (by invitation), Discussion by J William Hinton e] Dislocation of the cervical vertebrae Philip D Allen, Discussion by Byron Stookey, f] X-ray diagnosis of prolapse of the gastric mucosa, Benjamin Copleman (by invitation), Discussion by John R Carty ¶ Papers of the evening—a] Surgery in alcoholics, George A Koenig,

Discussion by John A MacLean (by invitation), b] Modern treatment of burns, Richard J O'Connell, Jr, Discussion by Fenwick Beekman ¶ General discussion ¶ Executive session

FEBRUARY 8—*Neurology and Psychiatry* Reading of the minutes ¶ Papers of the evening—a] The drama as a therapeutic measure in adolescents, Frank J Curran, Discussion, Jacob L Moreno (by invitation), John Levv (by invitation), Thomas K Davis, b] The psychology of schizophrenia, Paul Schilder, Discussion by Leland E Hinsie, Abraham A Brill, Nolan D C Lewis (by invitation), c] Fear as a therapeutic agent, Oskar Diethelm (by invitation), Discussion by Edwin G Zabriskie, Clarence P Oberndorf ¶ Executive session

FEBRUARY 10—*Pediatrics Residents' Program* Papers of the evening—a] Cornell University Medical College A case with unusual intracranial lesion, Charles J Baker (by invitation), Discussion, Samuel Z Levine, b] Long Island College of Medicine Hirschsprung's disease an acute abdominal emergency with temporary diabetes mellitus four years after lumbar sympathectomy, Vincent Tosti (by invitation), Discussion, Charles A Weymuller (by invitation), c] New York Medical College Fusio spirochetal bronchitis, C Michael Witzberger (by invitation), Discussion, J T Simonson (by invitation), d] New York Post-Graduate Medical College The serum treatment of meningococcic meningitis, Charles J Leslie (by invitation), Discussion, Marshall C Pease, e] New York University Medical College A case of pellagra in a colored child, Samuel Prince (by invitation), Discussion, Charles Hendee Smith, f] College of Physicians & Surgeons Control of repeated attacks of paroxysmal tachycardia with meclothyl, F Howell Wright (by invitation), Discussion, Rustin McIntosh ¶ Executive session

FEBRUARY 15—*Medicine* Reading of the minutes ¶ Papers of the evening Symposium on allergy—a] Recent advances in allergy, Maximilian A Ramirez, Discussion, Will Cook Sprain, b] Clinical manifestations of skin allergy, J Gardner Hopkins, Discussion, Aaron Brown, c] Bacterial aspects of allergy, William S Thomas, Discussion, Maximin de Mouy Touart, d] Allergy of the respiratory tract, Robert A Cooke, Discussion, Horace S Baldwin ¶ General discussion

FEBRUARY 16—*Genito-Urinary Surgery* Reading of the minutes ¶ Presentation of cases—Hydatid cysts of the kidney, Luis A Surricco, Montevideo (by invitation) ¶ Paper of the evening—Recent chemotherapy in infections of the urinary tract, William F Braunsch (by invitation) ¶ Discussion, Henry G Bugbee, Roy B Henline, Alexander R Stevens, Stanley R Woodruff

FEBRUARY 16—*Otolaryngology* Reading of the minutes ¶ Presentation of cases—a] Bacterial otitic meningitis, Edward R Roberts (by invitation) ¶ Papers of the evening—a] Primary carcinoma of the external auditory canal and meatus, Otto C Risch, James R Lisa, b] The role that surgery of the paranasal sinuses plays in the asthmatic child, preliminary report, Raymond C Creasy (by invitation) c] Surgical indications in sinusitis, Daniel S Cuning (by invitation), d] Sinus complications and their surgical treatment, Robert E Buckley ¶ Discussion, Duncan MacPherson ¶ General discussion

FEBRUARY 18—*Combined Meeting of the Section of Orthopedic Surgery and the New York Roentgen Society* Papers of the evening—a] Herniation of the nucleus pulposus A clinical study (30 minutes), Byron Stooker, b] Radiotherapy of bone tumors (30 minutes), Maurice Lenz, Arthur Purdy Stout c] Uses of the osseous system (20 minutes), Richard A Rendich, Bernard Ephrenpreis ¶ General discussion

FEBRUARY 21—*Ophthalmology* Instructional hour—Perimetry, Ralph Lloyd ¶ Slit lamp demonstration, Milton L Berliner, Wendell L Hughes, Girolamo Bonaccolto, Gordon M Bruce ¶ Reading of the minutes ¶ Presentation of cases—a] Suprasellar meningioma, Kaufman Schliek, b] Total symblepharon with plastic repair, Walter Griffev (by invitation), c] Conjunctival cyst simulating prolapse of lachrymal gland, James W Smith ¶ Papers of the evening—a] Subconjunctival section of the ductules of the lachrymal gland as a cure for epiphora, P Chalmers Jameson (by invitation), b] Obstetrical ophthalmology, Dewey Katz (by invitation), Discussion, Alvin J B Tillman, Frances Richman (by invitation)

FEBRUARY 22—*Obstetrics and Gynecology* From *The Woman's Hospital, New York City* Case Report—Unusual irregularity of the fetal heart, Lyman Burnham (by invitation) ¶ Papers of the evening—a] Hemorrhage in late pregnancy, labor, and the puerperium, Ralph L Barrett, b] Cystocele its pathology and reconstruction, Joshua W Davies (by invitation) c] Syphilis its relation to obstetrics and gynecology, Joseph N Nathanson (by invitation), d] Postoperative wound disruption, Olaf Severud (by invitation) e] Urological complications following complete hysterectomy, Arthur J Murphy

FEBRUARY 23—*Special Joint Meeting of the Section of Pediatrics and The Progressive Education Association* Symposium on early habit formations in relation to later social adjustments—a] From the viewpoint of the pediatricist, Bronson Crothers, Harvard Medical School (by invitation) b] From the viewpoint of the educator, Caroline B Zachry, Ph D, Progressive Education Association (by invitation), c] From the viewpoint of the mental hygienist, William Blatz, St George's School, Toronto (by invitation) d] From the viewpoint of the psychiatrist, Howard W Potter e] A coordination, Herbert B Wilcox

## AFFILIATED SOCIETIES

FEBRUARY 16—*New York Section of the Society for Experimental Biology and Medicine* Cathaphoretic separation of toxic components of moccasin venom, Walter Marx (by invitation), Samuel M. Peck ¶ The effect of total thyroidectomy upon the production and maintenance of experimental hypertension, Frank Glenn, Earl P. Lasker (Introduced by Bruce Webster) ¶ The use of calcium chloride in the relief of chills following serum administration, Paul B. Beeson, Charles L. Hargland (Introduced by O. T. Avery) ¶ Feeding glucose to the diabetic, Albert A. Epstein, Milton D. Feltenstein (by invitation) ¶ Vagal innervation of the dog's stomach Demonstration of its incompleteness in the Pavlov pouch, Edward E. Jemerin (by invitation), Franklin Hollander ¶ A method for the separation of micro-organisms from large quantities of broth culture, Jonas E. Salk (Introduced by R. Keith Cannon)

*New York Roentgen Society* On account of the joint meeting of the New York Roentgen Society with the Section of Orthopedic Surgery, February 18, no meeting of the New York Roentgen Society was held on Monday, February 21

FEBRUARY 24—*New York Pathological Society in affiliation with The New York Academy of Medicine* Case reports— a) Nephrosis due to carbon tetrachloride, Hans Smetana (by invitation) b) An unusual case of calcification of the myocardium with subsequent infection, Maurice N. Richter ¶ Papers of the evening— a) The prognostic significance of intracellular carminophilic material in carcinoma of the female breast, Virginia Kneeland Frantz, b) Observations on immunization with hemolytic streptococci in relation to virulence, D. Murray Angervine ¶ Executive session

## MEMBERS ELECTED

JANUARY 6, 1938

Bourdon M. Bosworth, 58 East 65 Street  
James Arnold Brussel, Brentwood I I  
Charles Walter Clarke, 50 West 50 Street  
John D. Currence, 219 West 44 Street  
Wade Duley, 60 East 96 Street  
Albert C. Herring, 15 East 77 Street  
Francis D. Huber, 9 East 96 Street  
Ed. Hotchkiss Irvine, 1040 Fifth Avenue  
William S. MacComb, 772 Madison Avenue  
Clement B. Masson, 405 East 54 Street

Vincent P. Mizzola

133 Clinton Street Brooklyn

Claude W. Munger, 421 West 113 Street

Alfred Rommoff, 23 East 74 Street

Archibald McIntyre Strong

150 Fort Washington Avenue

FEBRUARY 3, 1938

Vitus William Badia, 230 East 48 Street

William Bertram

12 Chester Avenue, White Plains

McKeen Cattell, 1300 York Avenue

D. Stoddard Dooman

82 Second Street, Garden City

Ira McLean, 153 East 72 Street

Wilson G. Smilie, 1300 York Avenue

Louis J. Soffer, 1165 Park Avenue

Harry E. Ungerleider, 393 Seventh Avenue

## DEATHS OF FELLOWS

ARMSTRONG, ARTHUR SOLER 103 East 65 Street, New York City, born in Rome, New York, January 14, 1879, died in New York City, January 13, 1938 graduated in medicine from Cornell University Medical College in 1904 elected a Fellow of the Academy February 7, 1918

Dr Armstrong was surgeon to the Knickerbocker and Misericordia Hospitals. He was a Fellow of the American College of Surgeons, the American Medical Association and a member of the New York County and State Medical Societies.

BROWN, LAWRENCE 24 Church Street, Saratoga Lake, New York born in Baltimore, Maryland, September 29, 1871 died in Saratoga Lake, New York, December 26, 1937 received the degrees of Bachelor of Arts in 1895 and Doctor of Medicine in 1900 from the Johns Hopkins Medical School elected a Fellow of the Academy November 4, 1915

Dr Brown was visiting physician to the Trudeau Sanatorium, Saratoga and consulting physician to the Waverly Hills Sanatorium, Louisville, Kentucky. He was a member of the Board of Trustees of the New York State Hospital for Incipient Tuberculosis at Rav Brook, a member of the Board of Trustees of Potts Memorial Hospital at Livingston, a member of the Advisory Council of the Henry Phipps Institute at the University of Pennsylvania, and of the Advisory Council of the Milbank Foundation.

Dr Brown was a Fellow of the American Medical Association and a member of the Association of American Physicians, the American College of Physicians, the American Clinical and Climatological Association and its president in 1920 the American Association for Thoracic Surgery, the National Tuberculosis Association and its president from 1919 to 1923, the American Public Health Association, and the County and State Medical Societies.

He was the author of the book "Rules for Recovery from Tuberculosis" and contributed many articles for journals on this topic.

FEIT, HERMANN 952 Fifth Avenue, New York City, born in Colfeuce on the Rhine, Germany, August 29, 1890 died in New York City, January 19, 1938 graduated in medicine from the University of Bonn, Germany, in 1918 elected a Resident Fellow of the Academy January 5, 1928, and designated a Fellow in Dermatology and Syphilology in 1933.

Dr Feit was dermatologist to the Vanderbilt Clinic, dermatologist and syphilologist to the Ruptured and Crippled Hospital and consulting dermatologist to the Englewood and Glenville Hospitals of New Jersey. He was a Fellow of the American Medical Association and a member of the County and State Medical Societies.

GOLDSTEIN, ISADORE 1095 Park Avenue, New York City, born in New York City in 1887 died in New York City, December 23, 1937, graduated in medicine from Cornell University in 1904, elected a Fellow of the Academy May 2, 1918.

Dr Goldstein was ophthalmic surgeon and Associate in ophthalmology to the Mount Sinai Hospital, senior assisting surgeon to the New York Eye and Ear Infirmary and consulting ophthalmologist to the Sindenham Hospital.

He held a certificate from the American Board of Ophthalmology and was a member of the American Academy of Ophthalmology and Otolaryngology and the County and State Medical Societies.

LEVY, RALPH J. 25 Central Park West, New York City, born in New York City, February 10, 1888, died in New York City, December 12, 1937, graduated in medicine from the New York Homeopathic Medical College and Flower Hospital in 1914 elected a Fellow of the Academy January 6, 1927.

Dr Levy was a Fellow of the American College of Surgeons, the American Medical Association, and a member of the County and State Medical Societies.

## MILESTONES IN MEDICINE

UNDER this appropriate title the 1936-37 series of the Laity Lectures of The New York Academy of Medicine is published. The book contains a brief introduction by James Alexander Miller, President of the Academy, and seven addresses on the historical and psychological aspects of medicine.

We have read each of these with pleasure and profit and are impressed with the ability displayed by these distinguished scientists in presenting the results of intricate research in a form and style agreeable to laymen as well as physicians.

The names of the contributors and the titles of the addresses may suggest in some measure the reason for the widespread interest manifested this year in the publication of the Laity Lectures, but the enjoyment derived from reading this little book indicates the well founded basis for its popularity.

The contributors to "Milestones in Medicine" and the subjects of the addresses are

SMITH ELY JELLIFFE  
CHARLES R. STOCKARD  
KARL VOGEL  
FREDERICK TILNEY  
HENRY E. SIGERIST  
NEWTON E. WAYSON  
WALTER TIMME

The Historical Background of Psychiatry  
The Mechanisms of Heredity  
Medicine at Sea in the Days of Sail  
The Evolution of the Human Brain  
The History of Medical History  
The History of Leprosy  
The Story of the Glands of Internal Secretion

The book is published by the D. Appleton-Century Company, contains 276 pages and costs two dollars.

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## POSTPONEMENT OF EXHIBITION OF PORTRAITS

THE exhibition of portraits of Presidents of The New York Academy of Medicine announced for February 14-25 has been postponed to April 18-30. The Academy extends an invitation to physicians and to the general public to view this exhibition.

BULLETIN OF  
THE NEW YORK ACADEMY  
OF MEDICINE



APRIL 1938

THE PASTEUR-MEYERHOF REACTION  
IN MUSCLE METABOLISM

*Harvey Lecture, November 18, 1937*

EINAR LUNDSGAARD

Institute of Medical Physiology University of Copenhagen

BEFORE ENTERING on my subject, may I say that this title is not quite adequate. The Pasteur-Meyerhof reaction is the main subject of my lecture, but it is my intention at the same time to deal with the metabolism of the aerobically working muscles on a somewhat broader basis than indicated by the title.

It is an assumption frequently encountered in physiological literature, that the metabolism of the aerobically working muscles is a pure carbohydrate metabolism. That assumption cannot have originated from the experience gained in metabolism determinations during muscular exercise. It is a familiar fact that even heavy muscular exercise can be performed on a pure fat diet, and with a respiratory quotient which indicates a combustion almost entirely of fat. Experiments by Krogh and Lindhard<sup>1</sup>, and recently by their pupils<sup>2,3</sup>, have demonstrated this very convincingly. Of course, the fact that hard muscular work can be performed under conditions in which the respiratory quotient is low, does not disprove the belief

that the working muscles oxidize carbohydrate only, for the possibility certainly exists that in the organism—presumably in the liver—there is a process of carbohydrate formation from fat, so that the muscles may very well be supplied with carbohydrate even in conditions in which the organism as a whole is metabolizing fat alone. However, this purely hypothetical possibility can scarcely explain why the conception of a pure carbohydrate metabolism in the aerobically working muscles is so hard to eradicate, as actually seems to be the case. From this remark perhaps you will anticipate that I think that this conception should be discarded.

If we endeavor to discover how such a conception arose, and whence it has obtained sustenance all this time, we shall quickly find that the conception of a pure carbohydrate metabolism in the striated muscles arises from, and is supported by, the experience gained in experiments on the chemistry of isolated muscles, mainly the isolated muscles of cold-blooded animals.

The first to make convincing demonstrations of the connection between the mechanical function of muscles and a production of lactic acid, i.e., a carbohydrate metabolism, were Fletcher and Hopkins<sup>4</sup>. At this juncture, however, perhaps I may be permitted to say that probably the first to express the supposition of a connection between a formation of lactic acid in the muscles and their work was the Swedish chemist Berzelius. Du Bois-Reymond<sup>5</sup> tells us that in 1841 Berzelius stated that he had noticed that muscles from animals which had been hunted before being killed, seemed to contain very considerable quantities of lactic acid, whereas muscles from partly paralyzed extremities seemed to contain only small quantities of that substance. Nevertheless, it was of course the famous investigations of Fletcher and Hopkins<sup>4</sup> that brought lactic acid formation into the prominent position in muscle chemistry which it has since preserved almost intact. Their experiments showed how lactic acid, which had accumulated in muscle during work, would disappear after the work when the muscle was kept under aerobic conditions. However, the explanation of the disappearance of the lactic acid under aerobic conditions stands to the credit of Meyerhof<sup>6</sup>, from whose fine experiments it appeared, that under aerobic conditions lactic acid can be rebuilt into the glycogen from which it was originally formed. In forming an estimate of the value of these investigations, admirable as they are in themselves in their more general biological applicability, it must be remembered that the direct demonstration of the resynthesis of glycogen from lactic acid

can be made only under conditions in which the formation and the removal of the lactic acid are separated in time. Finally, it must be borne in mind that, judging from these experiments—on cold-blooded animals only, it is true—the resynthesis of lactic acid to glycogen seems to be a fairly slow process. It is now easy to see why Meyerhof's demonstration of a carbohydrate cycle  $\text{glycogen} \rightleftharpoons \text{lactic acid}$  has become generalized, in the sense that such a cycle has been accepted as an explanation both of the so-called Pasteur reaction in yeast, and of the parallel circumstance that no lactic acid formation can be demonstrated in aerobically working muscles. If the theory should be maintained that a breakdown of glycogen to lactic acid is an absolutely essential phase in the chemistry of muscle contraction, it would become absolutely necessary to assume that a formation of lactic acid does take place also in aerobically working muscles, indeed a lactic acid formation of the same degree as that taking place in a muscle which, under anaerobic conditions, works with the same intensity. In actual fact, the entire conception of the central rôle of lactic acid in the chemistry of muscle contraction only became possible when Meyerhof's demonstration of the carbohydrate cycle permitted the assumption that the reason why no lactic acid formation can be demonstrated in an aerobically working muscle is, that the lactic acid actually formed is rebuilt into glycogen as quickly as it is formed. That the theory concerning the rôle of lactic acid formation in muscle contraction (for which Meyerhof fought, and especially in his controversy with Embden fought so energetically) necessitated this interpretation of the Pasteur-Meyerhof reaction in the muscles, and thereby made the same interpretation of the Pasteur reaction in yeast probable, is undoubtedly the psychological reason why this interpretation was accepted without hesitation. For actually, the direct proofs of the correctness of this view are not strong.

By the Pasteur reaction is understood, as you know, the circumstance that under aerobic conditions fermentation recedes, in some cases completely, so that the yeast has a metabolism that is purely oxidative. As far as we can see, Pasteur himself conceived fermentation and oxidation as two mutually independent metabolic processes, in the sense that they are not coupled processes, but two reactions which can replace each other. Nowhere does Pasteur express the supposition that the cause of the recession of fermentation under aerobic conditions is that the terminal products of the fermentation process, or intermediate products, are resynthesized into carbohydrate. That interpretation is Meyerhof's<sup>6</sup>



That the so-called oxidation coefficient, or the Meyerhof coefficient, is of fairly constant value, has been regarded as evidence that Meyerhof's interpretation of the mechanism of the Pasteur reaction is correct, that is, as evidence of a coupling between oxidation and resynthesis into carbohydrate. By the oxidation coefficient is understood the ratio between the recession of the fermentation or glycolysis under aerobic conditions and the oxidation intensity. The determination of this coefficient is of course of value only, when it concerns yeast or tissues in which a residue of the fermentation or glycolysis persists under aerobic conditions. It must be pointed out, however, that this coefficient displays nothing like pronounced constancy. And in those cases in which there has been an assumption that a conformity exists between the oxidation coefficient in yeast and tumor tissue, and the oxidation coefficient in muscle, it must be pointed out that no such conformity has been proved. The oxidation coefficient for muscle has been calculated on the basis of experiments on the directly demonstrable resynthesis of lactic acid to glycogen in muscle which, after having worked anaerobically, is supplied with oxygen. In the first place, the ratio found in such experiments between "disappeared lactic acid" and oxidation (oxygen consumed during restoration) is not at all constant, and in the second place, the question of how the basal metabolism of the muscle in the very long period of recovery is to be accounted for in the calculation is a most uncertain one. Finally, it must be pointed out, and that is perhaps the most important point, that the calculations are made on the supposition that the resynthesis of lactic acid is the only endothermic reaction in recovering muscles in which the oxidation energy is engaged, whereas we now know that other endothermic reactions take place (resynthesis of creatine phosphoric acid). All in all, it must be said that the postulated constancy of the oxidation coefficient in various tissues does not contain any demonstrable evidence that the Pasteur-Meyerhof reaction depends upon a coupling between a resynthesis of carbohydrates on the one hand, and oxidations on the other.

It has been asserted that the correctness of Meyerhof's interpretation of the mechanism of the Pasteur-Meyerhof reaction is proved by Meyerhof's experiments with yeast<sup>7</sup>, the object of which was to show more directly an oxidative resynthesis to carbohydrate of the final product of the fermentation process, alcohol. Thus these experiments would correspond exactly with the demonstration of the oxidative resynthesis of lactic

acid to glycogen in muscles during aerobic recovery. Whereas in Meyerhof's muscle experiments<sup>6</sup> it has been possible to show directly an increase of the glycogen content in the muscles, proceeding in equal pace with the disappearance of the lactic acid, no corresponding direct demonstration has been made of an increase of the carbohydrate content in yeast respiring in an alcoholic medium. On the other hand, Meyerhof<sup>7</sup> under such conditions found a very low respiratory quotient, the respiratory quotient when yeast oxidizes alcohol usually being as low as 0.3. Meyerhof took this low quotient to be evidence of a resynthesis of carbohydrate, a reaction having the character of a partial oxidation and therefore bound to give a low respiratory quotient. From the respiratory quotient Meyerhof calculated the ratio between oxidized and resynthesized alcohol, that is to say the "oxidation coefficient", and found that it was of the same value as the oxidation coefficients in yeast calculated in other ways and the corresponding coefficients in tumor tissue and muscle.

I have made experiments of the same kind<sup>8</sup>, and have been in a position to confirm the regular occurrence of very low respiratory quotients when yeast respire in alcoholic medium, at the same time, however, I consider I have been able to show that Meyerhof's interpretation of these very low quotients is incorrect.

If a moderate quantity of alcohol is employed in the medium, and the experiments are continued for some hours, it will be found that in the first periods the respiratory quotient is very low. At a certain point of time, dependent on the amount of alcohol added to the samples, the respiratory quotient rises quickly, rather suddenly and reaches unity. It can now be shown that as long as the respiratory quotient remains low, an organic acid accumulates in the samples, and, when the quotient rises, the organic acid begins to disappear while simultaneously the intensity of oxygen absorption begins to decrease. If the experiments are discontinued at a time when alcohol still remains in the samples, it is possible by direct alcohol determinations to establish the amount of alcohol that disappeared during the experimental period. From the carbon dioxide output and the directly determined acid formation (determined as increase in ether-soluble acids), it is possible to calculate the total amount of alcohol oxidized completely and that oxidized to organic acid. If the sum of these two values is compared with the directly determined loss of alcohol, we find that the latter is somewhat greater than the sum of the other two values. Thus some alcohol seems to have disappeared which cannot be

accounted for, and which consequently may have been converted into carbohydrate. This quantity, however, is much smaller in proportion to the alcohol oxidation than that calculated by Meyerhof. The latter calculated the ratio between alcohol resynthesized into carbohydrate and alcohol oxidized at 3:1, according to my experiments the ratio cannot be more than 1:1, that is to say a ratio of dimensions quite different from the oxidation coefficient found previously. There can be no doubt that the very low respiratory quotients are mainly a result of the fact that alcohol is oxidized by yeast in two phases, the alcohol first being converted into organic acids (presumably acetic acid), which thereupon are oxidized completely.

TABLE I

		$CO_2$ cmm	$O_2$ cmm	RQ	Alcohol completely oxidized mg%	Alcohol oxidized to acid mg%	Alcohol disappeared calculated mg%	Alcohol disappeared determined mg%	Alcohol oxidized to carbo- hydrate mg%
POISONED SAMPLES									
Exp	1	93	280	0,33	9,5	21,1	30,6	31	0
"	2	72	289	0,25	7,4	29,0	36,4	34	-2,4
"	3	85	288	0,30	8,7	27,6	36,3	33	-3,3
"	4	116	348	0,33	11,9	23,6	34,5	38	3,5
"	5	117	338	0,35	12,0	24,4	36,4	33	-3,4
NORMAL SAMPLES									
Exp	1	167	499	0,34	17,1	22,1	39,2	56	16,8
"	2	178	500	0,36	17,8	23,4	41,2	58	16,9
"	3	173	495	0,35	17,7	25,8	43,5	56	12,5
"	4	130	349	0,38	13,3	14,7	28,0	38	10,0
"	5	138	372	0,37	14,1	17,0	31,1	35,2	3,9

As I attach some importance to these experiments I shall take the liberty of going into them a little further and showing you some of the numerical data. The experiments were carried out partly with normal yeast and partly with yeast poisoned with iodo-acetic acid, whereby the ability of the yeast to ferment is destroyed. In table I you see the results of five experiments with normal yeast and five with poisoned yeast. The last column contains the calculated formation of carbohydrate. You will observe that in the poisoned samples, which by the way have a rather lower oxygen absorption than the normal samples, there is no evidence of any carbohydrate formation, whereas in the normal samples there is. The ratio of alcohol oxidized to alcohol resynthesized appears from a comparison between the fourth and the last column. There is no difference, how-

ever, in the respiratory quotient in the two series of experiments. Thus we may say that the respiratory quotient in the normal samples does not appear to reflect any carbohydrate synthesis. Only when we make the rather complicated calculation, the elements of which are the output of carbon dioxide, the alcohol determinations and those of the ether-soluble acids, is any carbohydrate formation revealed. In advance it was reasonable to assume that there would be no carbohydrate formation, at any rate in yeast poisoned with iodo-acetic acid, and no such formation could in fact be demonstrated. Therefore, the consequence of the close agreement between the value of the respiratory quotient and its variations in experiments with normal and poisoned yeast is, that we cannot feel fully convinced that carbohydrates really are formed in the normal samples.

TABLE II

						POISONED		NORMAL			
						<i>mm</i> <i>CO</i> <sub>2</sub>	<i>mm</i> <i>O</i> <sub>2</sub>	<i>RQ</i>	<i>mm</i> <i>CO</i> <sub>2</sub>	<i>mm</i> <i>O</i> <sub>2</sub>	<i>RQ</i>
						37	114	0,32	39	112	0,35
						25	110	0,23	44	132	0,33
1 hr	10 min	to	1 hr	40 min		29	101	0,29	61	150	0,41
1 "	45 "	"	"	2 " 15 "		43	80	0,54	84	86	0,98
2 "	20 "	"	"	2 " 50 "		47	55	0,86	76	76	1,00
2 "	55 "	"	"	3 " 25 "		40	43	0,93	30	29	1,03
3 "	30 "	"	"	4 " 00 "		40	41	0,98	21	21	1,00
4 "	00 "	"	"	4 " 30 "		31	33	0,94	9	9	1,00
4 "	30 "	"	"	5 " 00 "		28	27	1,03	8	8	1,00
5 "	00 "	"	"	5 " 30 "		16	15	1,05			
5 "	30 "	"	"	6 " 00 "		8	8	1,00			

In table 2 I have shown the results of two experiments with normal and poisoned yeast, continued so long that the alcohol disappeared entirely, the oxidation intensity has fallen to the same low values as are found for yeast suspended in pure phosphate buffer. In other words, the experiments were continued till the samples were practically free of substrate. You will observe that the quotient rises through the experiment—rather more gradually in the poisoned sample than in the normal one. If we calculate the quotient for the total experimental period we get 0.54 for the poisoned sample and 0.59 for the normal one, that is to say, quotients that are rather below the quotient for a pure alcohol oxidation, but of almost equal size in the two samples. Were the reduction of the quotient due to a formation of carbohydrate, the latter would, according to these experiments, in which the calculation is not very complicated, be just as pronounced in

the poisoned sample as in the normal. There is nothing to show that the organic acid in the normal sample passes through a conversion to carbohydrate before being completely oxidized. I therefore consider that my experiments entitle me to conclude that, even if one cannot definitively deny the possibility of a synthesis of alcohol to carbohydrate, no real evidence can be produced to show that such a process does occur. If a synthesis of alcohol to carbohydrate does occur, at any rate the oxidation quotient of that process has a value quite different from the one Meyerhof<sup>7</sup> calculated, and from the one which can be calculated on the oxidation intensity and the recession of the fermentation when yeast respire in carbohydrate medium. Consequently, nothing in these experiments tends to show that Meyerhof's interpretation of the mechanism of the Pasteur-Meyerhof reaction is correct, and therefore there is some justification in asking if there is any reason for continuing to accept that interpretation.

You will recollect my saying that Meyerhof's interpretation was, so to speak, necessary if the conception of lactic acid formation as an essential part of the chemistry of muscle contraction were to be maintained. Here again it is not possible today to discern any reason for persisting in this interpretation.

At the present moment it is doubtless generally acknowledged that the formation of lactic acid is not essential to the chemistry of muscle contraction. I believe there is reason for saying that the introduction of iodo-acetic acid poisoning in muscle chemistry has contributed very considerably to the rapid and complete acceptance of that view.



Fig 1

Typical series of isometric twitches performed by a gastrocnemius muscle poisoned with iodoacetic acid  
Muscle weight 0.7 g Distance between two horizontal lines 200 g tension

Though for obvious reasons the investigations on the chemical changes in working muscle poisoned with iodo-acetic acid holds a favorite place in my heart, on this occasion I shall deal only briefly with the results achieved from the experiments<sup>9,10</sup>

The effect of iodo-acetic acid is an inactivation of the enzyme system involved in the formation of lactic acid. A muscle poisoned with this compound is capable of performing a series of 60-90 twitches anaerobically without any formation of lactic acid taking place and then goes into rigor (Figure 1). The twitches are in all respects completely normal, that is in respect of latent time, duration of the twitch, heat formation, development of tension and action current. The total amount of work which an isolated poisoned muscle is able to perform is, however, smaller than that which a normal one can perform. This may be expressed by saying that the energy reserve available under anaerobic conditions is decreased when the ability to form lactic acid is abolished. These facts alone give a clear conception of the rôle played by the formation of lactic acid in the chemistry of muscle contraction. The formation of lactic acid is not a necessary link in that chemistry, and consequently this process cannot have any direct connection with what we may call the mechanism of contraction. On the other hand, the formation of lactic acid or the ability to form lactic acid must be looked upon as an important energy reserve available under anaerobic conditions.

When we determine the chemical changes occurring in an iodo-acetic poisoned muscle during stimulation, we find that the intensity of the breakdown of creatine phosphoric acid is greater than in a normal muscle. When a poisoned muscle has performed a series of 60-90 twitches the muscle is exhausted and goes into rigor. At this stage the total amount of creatine-phosphoric acid has been broken down, and, moreover, the adenylic phosphoric acid has been broken down too. In a normal muscle only about one-third of the creatine phosphoric acid has been broken down after the performance of 60-90 twitches. The energy liberated during the anaerobic work of a poisoned muscle undoubtedly originates from the breakdown of creatine phosphoric acid. Having regard to the time I have at my disposal I shall not venture upon a discussion of this statement.

There is one point, however, elucidated through my experiments with muscle poisoned with iodo-acetic acid, which I would like to deal with more fully, as it is of essential importance to the subject of my lecture today.

When two symmetrical sartorii, which have been poisoned by soaking in Ringer solution to which iodo-acetic acid has been added, are stimulated, one in oxygen and the other in nitrogen, it is seen that the muscle

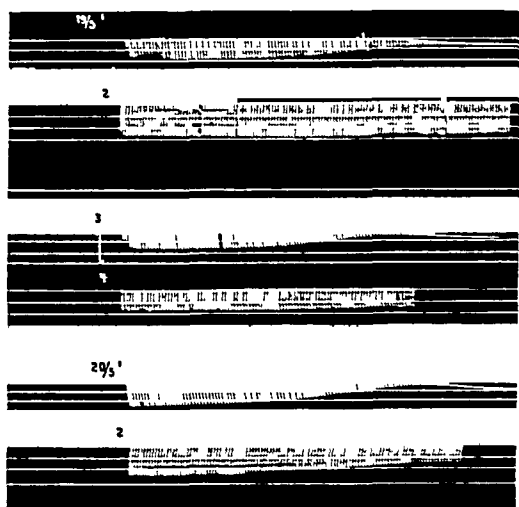


Fig 2

Series of isometric twitches performed by symmetrical IAA poisoned sartorii muscles one stimulated in nitrogen (upper ones) and one stimulated in oxygen (lower ones)

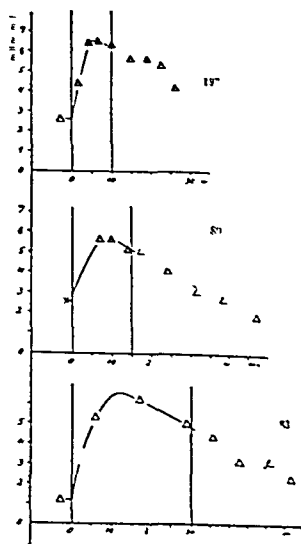


Fig 3

Changes in blood lactate concentration during and after muscular exercise. Duration of work indicated by interval between the two vertical lines. Working intensity in all experiments 000 kgm/min

supplied with oxygen is capable of performing much more work than the muscle stimulated in nitrogen. The latter will be completely exhausted and go into rigor at a time when the other muscle is still giving maximum tension. This is illustrated by these records, from experiments of the kind I have described (Figure 2). If the muscle which has worked aerobically is analyzed at a point of time when it has performed a much greater work than the completely exhausted anaerobic muscle, it will be found still to contain considerable quantities of creatine phosphoric acid. This means that there can be no doubt that energy arising from oxidation processes can be utilized in the production of mechanical energy, that is to say, utilized for the performance of exterior work, even under circumstances where there can be no question of intermediate lactic acid formation. That such a formation is out of the question, may be concluded with certainty from the fact that the symmetric muscle, working under anaerobic conditions, passes through the series of twitches in a manner characteristic of a muscle completely poisoned with iodo-acetic acid.

We cannot say with certainty whether under these circumstances the oxidation energy is utilized through an oxidative resynthesis of creatine phosphoric acid, or is transferred more directly to what we may call

"the mechanism of contraction" As long as it has not been shown that the breakdown of creatine phosphoric acid is not a necessary link in the chemistry of muscular contraction, I shall consider it most natural to assume that the oxidation energy is utilized through an oxidative resynthesis of creatine phosphoric acid, but perhaps the day is not far distant when it will be possible to show that the breakdown of creatine phosphoric acid is not an obligatory process in the chemistry of muscle contraction, just as it has been possible to show this as far as lactic acid formation is concerned

To my mind the following conclusions are justified from the results obtained in experiments with muscles poisoned with iodo-acetic acid

The formation of lactic acid is not an essential element in the chemistry of muscle contraction, nor is an intermediate lactic acid formation a necessary element in the utilization of oxidation energy for the production of mechanical energy in the muscles

Accordingly, the experience gained in experiments with isolated muscle no longer provides a reason for assuming that in aerobically working muscle there is a constant intermediate formation of lactic acid which, as quickly as it is formed, is resynthesized to glycogen Another way of expressing this is, that no reasons can be found for accepting Meyerhof's interpretation of the Pasteur-Meyerhof reaction in aerobically working muscles On the other hand we can still speak of a Pasteur-Meyerhof reaction in aerobically working muscles, as by this we merely understand the circumstance that the formation of lactic acid decreases in the muscles under aerobic conditions

The question may now be asked If we cannot accept the factors which originally supported the "classic" view of the Pasteur-Meyerhof reaction in the striated muscles, then are there any others to be advanced in favor of that view? I do not think so

There are experiments on the blood lactic acid concentration in man during and after muscular exercise, and these experiments to my mind rather argue against the classic view of aerobic muscle metabolism Experiments of this kind were made by O Bang<sup>11</sup>, partly in Krogh's institute and partly in mine

By means of a micro-method, which makes it possible to measure the lactate concentration in blood samples of only 0.1 cc, Bang has followed the variations in the blood lactate concentration during and after exercise Thanks to the method employed, the concentration could be deter-



mined at short intervals, whereby a reliable curve was obtained for the variations. As far as the present subject is concerned, greatest interest attaches to those experiments in which the working intensity was such that a "steady state" was quickly arrived at. Figure 3 shows three curves from such experiments. It will be seen that immediately after the commencement of the exercise the blood lactate rises quickly and reaches a maximum in the course of from seven to ten minutes. Then the concentration begins to fall, even when the work is continued. This means, then, that even under conditions in which a steady state is arrived at for oxygen absorption, this does not happen with the lactic acid concentration, at any rate, not in the blood. In experiments in which the working intensity is less, and the primary increase of the blood lactate is consequently lower, the blood lactate falls even to basal values during the work. Even if we cannot assume that the blood lactate at any moment reflects the concentration in the working muscles, the falling blood curves to me are incompatible with the conception of a high, constant level in the working muscles throughout the working period. This applies especially to the experiments in which the blood lactate fell to basal values during the work. Now, this high and constant level is necessary if the classic view of the metabolism of the aerobically working muscles is to be upheld. According to that view, the assumed constant lactic acid production was supposed to lead in relatively few minutes to the attainment of a constant, increased lactate level in the active muscles, subsequently maintained throughout the "steady state." The constant level, it was thought, was attained by the rise in lactate concentration in itself inducing a rise in the intensity of oxidation, which in turn would involve a rise in the lactate resynthesis, until an equilibrium was established between production and resynthesis, at a level depending on the intensity of lactic acid formation, i.e., the intensity of work.

It is an outstanding feature of the curves in Figure 3 that the fall in blood lactate continues steadily after cessation of the work. This is difficult to reconcile with the conception that during work a very intensive production of lactic acid proceeds in the active muscles, but that this ceases simultaneously with the work. In that case one would expect to find a much quicker fall after work ceased. In reality, however, the three curves are almost identical, although they represent experiments with varying periods of work. The working intensity, on the other hand, was the same in all three experiments.

Personally, I am inclined to believe that Bang's interpretation of the experiments may be correct. According to Bang<sup>11</sup>, we must assume that an intensive formation of lactic acid takes place in the active muscles in the first minutes after the commencement of work. Presumably the reason is that it takes a certain time for the general and local circulations to adapt themselves to the increased demand for oxygen. Until the circulation is adjusted, the muscles work partly anaerobically, that is to say they utilize the anaerobically available energy depôt represented by the ability to form lactic acid. When the circulation is adjusted and the oxygen supply to the muscles is adequate, all formation of lactic acid ceases. Thus, at the commencement of work a depôt of lactic acid is formed in the active muscles. The size of this depôt is independent of the duration of the work, and solely dependent on the intensity of the work. The greater the intensity of the work, the greater quantity of lactic acid can be formed before the circulation has become adjusted.

However, even if there is much in favor of Bang's interpretation of the experiments, it must be said that not even that interpretation provides a fully satisfactory explanation of the circumstance that the fall of blood lactate continues steadily after cessation of work. The depôt of lactic acid which, according to Bang, is presumably formed in the active muscles during the first minutes of the work, must be imagined as being removed, partly by diffusion to the blood and from there to resting organs (principally the liver), partly by oxidation in the active muscles, and finally by resynthesis to glycogen in the active muscles. Whereas the latter process may well be a slow one, it is hard to understand that the oxidation of lactic acid in the active muscles does not proceed with considerable intensity, and especially with greater intensity during work, when metabolism is greatly increased, than after cessation of work. A dependence of the rate of lactic acid removal on the rate of metabolism actually has been demonstrated by Newman, Dill, Edwards and Webster<sup>12</sup>.

For this reason the fact that the blood lactate concentration may fall and even reach the basal level during the working period must be considered the most clearcut and consequently the most important result of the determinations of the blood lactate concentration during muscular exercise. As already mentioned this observation is incompatible with the classic view, according to which the metabolism of aerobically working muscles includes an obligatory intermediate lactic acid formation, which is balanced by an oxidative resynthesis of the lactic acid formed.

If now we return to the theory of a pure carbohydrate metabolism in the active muscles, it must be said that we have been unable to find any support for that theory in the experimental facts to which I have so far referred. This is a matter of considerable weight, as it eliminates the basis on which the theory to my mind has principally rested.

As I have laid particular stress on Meyerhof's interpretation of the Pasteur-Meyerhof reaction as a basis for the theory of a pure carbohydrate oxidation in aerobically working muscles, I should state at the same time that this interpretation, as indeed pointed out by Meyerhof too, does not require as an inevitable consequence that the metabolism of the active muscles be a pure carbohydrate oxidation. There is the possibility that the energy necessary for the endothermic lactic acid synthesis is produced by the oxidation, not of lactic acid or carbohydrate, but of fat or protein. This, however, does not alter the fact that Meyerhof's interpretation of the Pasteur-Meyerhof reaction has been regarded, and justly so I think, as an argument in favor of the assumption that the aerobically working muscles oxidize carbohydrate only.

Personally, I am inclined to the opinion that under such conditions, in which a formation of lactic acid actually takes place in the active muscles, the effect is that the oxidation proceeds entirely, or principally, at the expense of carbohydrate. In muscle working partly anaerobically there will be simultaneously lactic acid formation and oxidation. With very intense muscular exercise, which can only continue for a short time, the muscles will work to an appreciable degree anaerobically, and under just such conditions we see respiratory quotients of about unity, even when the quotient in rest lies much lower. Exactly the same thing is seen in the untrained subject during moderate work. Here, too, the respiratory quotient rises and remains high during the work, and simultaneously the blood lactate curve rises steadily as a sign that the muscles are working under partly anaerobic conditions.

If it be true, as I am inclined to believe, that lactic acid formation in the active muscles always leads to a high respiratory quotient, that is to say, to a combustion of carbohydrate, then it must be said that the low respiratory quotients seen in well-trained individuals on a fat diet, even during the performance of heavy work, also indicate that lactic acid formation is no obligatory link in the metabolism of the active muscles.

In conclusion, I would refer to a matter which, to me, has been of no small importance in judging the question of whether there is reason for

assuming that the metabolism of the aerobically working muscles is of specific character. For if it is, the most natural conclusion to draw is that it is a pure carbohydrate metabolism.

What I have in mind in this connection is the fact that the intensity of alcohol oxidation is not affected by muscular exercise.

I admit that the question of whether muscular exercise affects the intensity of alcohol oxidation has been answered variously by different authors. Nevertheless, in recent years more and more have accepted the view that the question must be answered in the negative. Among the experimental results which seem to show that the intensity of alcohol oxidation is not increased during muscular exercise, those of Nyman and Palmlov<sup>13</sup> are particularly convincing. As shown in experiments by Widmark<sup>14</sup> and others, however, the intensity of alcohol oxidation increases if metabolism is stimulated by dinitrophenol. This is also the case with thyroxin, according to Le Breton's preliminary experiments<sup>15</sup>. As alcohol oxidation represents up to 80 per cent of the basal metabolism, it would seem necessary to assume that part of the alcohol oxidation proceeds in the muscles. Therefore, the circumstance that an increased metabolism conditioned by muscular exercise does not increase the alcohol oxidation, whilst an increased metabolism produced by stimulating drugs does, seems to justify the conclusion that there is a specific difference between the metabolism of the resting muscles and that of the active muscles. In her monograph on alcohol oxidation Le Breton<sup>15</sup> actually arrives at a conclusion to this effect.

The circumstance that muscular exercise does not increase the intensity of alcohol oxidation might, however, have the explanation that neither in rest nor in work is alcohol metabolized directly in the muscles. If we imagine that alcohol oxidation is a specific function of the liver, it is easy to understand that an increased metabolism, due to an increased energy output in the muscles alone, does not increase the alcohol oxidation, whereas an increase of the metabolism intensity in all tissues, the liver included, does involve an increase of the alcohol oxidation.

One difficulty in assuming that oxidation of alcohol takes place only in the liver, is that the absolute quantity of alcohol oxidized in rest, as already stated, represents up to 80 per cent of the basal oxygen absorption, whereas in the liver the oxygen absorption amounts to only 30 or 40 per cent of the total basal oxygen absorption. Therefore, the assumption that alcohol oxidation is a specific liver function is conditional upon the

alcohol oxidation in the liver being a partial oxidation. A priori this idea cannot be dismissed, so much the more as partial oxidations are undoubtedly a characteristic feature in the metabolism of the liver. Even if we must also assume that the partially oxidized product formed in the liver is oxidized in all tissues, the muscles included, the primary oxidation in the liver will nevertheless be the limiting factor for the disappearance of alcohol in the whole system.

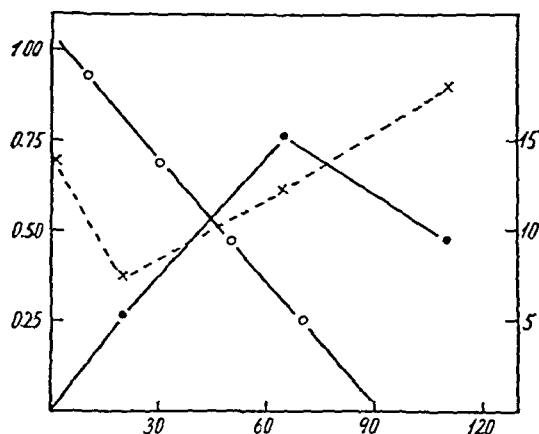


Fig 4

Exp on alcohol oxidation in isolated cat liver. Abscissas time in minutes. Left ordinate blood alcohol in per thousand and RQ. Right ordinate decrease in alkali reserve in cc carbon dioxide.

o — o blood alcohol

x — x RQ

● — ● acid formation (decrease in alkali reserve)

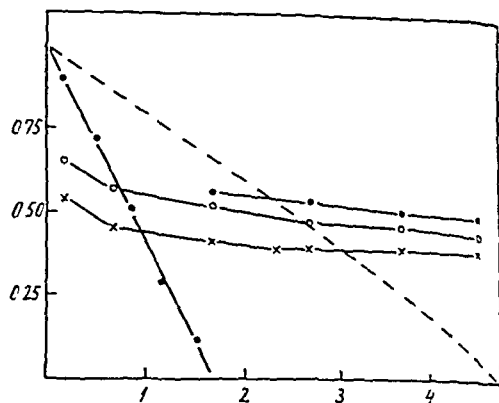


Fig 5

Exps on alcohol oxidation in isolated hind limb preparations. Abscissas time in hours. Ordinates blood alcohol in per thousand.

The three curves from three different experiments on hind limb preparations may be compared with a curve from an experiment on a liver (steep curve in the left part of the figure). As, however, the total amount of blood and tissue acting as solvent for the alcohol is three times as large in the hind limb preparations as in the liver preparations, the curves from the experiments on hind limb preparations actually must be compared with the broken curve.

That the supposition I have sketched is undoubtedly correct appears from certain experiments, as yet unpublished, which I have made on alcohol oxidation in artificially perfused isolated livers and hind-limb preparations. These experiments show that, in the liver alcohol undergoes a rapid but primarily only partial oxidation, whereas alcohol is not affected oxidatively at all in a hind-limb preparation. I shall take the liberty of showing you one or two curves from these experiments.

From the curves (Figure 4) it will be seen that the concentration of alcohol in the blood which is perfused through a liver falls quickly and at quite a constant rate. In the course of ninety minutes the entire quantity of alcohol (300 mg) has disappeared. The quantity of oxygen necessary to oxidize 300 mg alcohol completely is 440 cc. The oxygen absorption in the first ninety minutes was only 225 cc. After adding the alcohol, the

respiratory quotient falls from 0.69 to 0.37. This extraordinarily low quotient can only be explained as being due to incomplete oxidation. The lack of conformity between the quantity of disappeared alcohol and the absorbed quantity of oxygen may be explained in the same manner. In addition, the alkali reserve of the blood falls as a sign that acid products are being formed. When the alcohol has almost disappeared from the blood the alkali reserve begins to increase again. At the same time the respiratory quotient also rises, in the last determination in this experiment it reaches a value of 0.9. The increase of both the alkali reserve and the respiratory quotient must be assumed to be the result of a complete oxidation of the partially oxidized acid products formed in the first period after adding the alcohol. Incidentally, the similarity between an experiment of this kind and the yeast experiments previously mentioned is very striking.

The acid product formed in the liver experiments was not isolated and identified, but there can hardly be any doubt but that it was acetic acid. As acetic acid oxidizes with great rapidity in the living organism, it may be assumed that the acetic acid formed in the liver of an intact animal after the addition of alcohol is carried with the blood to all the different tissues and oxidized there.

In an isolated hind-limb preparation, alcohol is not affected oxidatively at all. After diffusion balance is established we see only a very slow fall in the blood alcohol concentration, a fall which does not exceed that seen in control experiments, in which the blood is circulated through the apparatus without passing living tissue (Figure 5).

The absolute quantity of alcohol oxidized in an isolated liver, per gram of liver tissue and minute, averages no more than 60 per cent of the quantity oxidized in the entire animal per gram of liver tissue and minute. Probably the cause of this is that the oxygen consumption of the liver, that is to say the metabolism intensity, falls distinctly in the course of the first five or ten minutes after isolation, so that we must also assume that the alcohol oxidation in a liver *in situ* is greater than in an isolated liver. The dominating rôle played by the liver in alcohol oxidation also appears from the fact that in eviscerated animals, the alcohol oxidation is extremely low and does not exceed 10 per cent of that of intact animals.

Thus the assumption that the oxidative metabolism of the active muscles is of a specific nature cannot find support in the circumstance that the intensity of alcohol oxidation is not increased during muscular

exercise, for the explanation is that alcohol is only primarily affected oxidatively in the liver, so that it is the primary oxidation in the liver that becomes the limiting factor in the alcohol oxidation of the total organism

As I have said, it may be assumed that the partially oxidized product formed in the liver can be oxidized completely in the various tissues, the muscles included I point this out, even if at the moment I cannot submit direct experimental evidence of it, because I am inclined to think that the same applies to the oxidation of fatty acids It is probable that the high-molecular fatty acids are not attacked, or not readily attacked oxidatively in the muscles On the other hand, partly oxidized products of the fatty acids, such as  $\beta$ -hydroxybutyric acid and other ketone bodies, are very readily oxidized in the muscles The fact that the oxidation of ketone bodies in the muscles is increased when the muscular metabolism is stimulated by work has been proved by experiments performed by Blixenchrone-Møller in my institute As these investigations have not yet been published I shall merely deal with them very broadly

If a cat-liver with a high fat content and poor in glycogen is artificially perfused, that liver will yield very considerable quantities of ketone bodies to the blood A liver from a cat which for some days has been treated with phloridzin, or a liver from a pancreatectomized cat, will in the course of two hours produce and transfer to the perfusion blood from 200 to 300 mg of ketone bodies or even more Now if such blood, which is rich in ketone bodies, is perfused through an isolated hind-limb preparation, the total quantity of ketone bodies will disappear in the course of one and one-half to two hours This means that the quantity of ketone bodies capable of being formed by a liver, even under circumstances in which that formation is profuse, can be got rid of at a rate corresponding to the rate of formation in a mass of muscle representing less than half of the total muscle of the animal If the experiment is performed so that the musculature of the hind-limb preparation is stimulated for a period of fifteen minutes, whereby the oxygen consumption of the preparation rises to about four times the basal consumption, all the ketone bodies will have disappeared in the course of only twenty to thirty minutes Therefore it is not open to doubt that ketone bodies are utilized as a fuel in muscular exercise It must be regarded as very improbable, not to say out of the question, that ketone bodies in an isolated muscle preparation are converted into carbohydrate before they are utilized

The assumption that fat oxidation proceeds in such a manner that the fatty acids in the liver undergo a partial oxidation to  $\beta$ -hydroxybutyric acid, and that it is this partly oxidized product which is utilized in the muscles, provides a natural and plausible explanation of the circumstance that the efficiency in muscular exercise is lower with pure fat combustion than with chiefly carbohydrate combustion, as has been proved by Krogh and Lindhard<sup>1</sup>

In the course of this lecture I have referred to experimental results from very different fields within physiology from research on the oxidative metabolism of yeast, from experiments with muscle poisoned by iodoacetic acid, the concentration of blood lactate in man during muscular exercise, the metabolism of alcohol in the organism, and the metabolism of fat in the isolated liver. To me, all these results, however different in nature they may seem, have been of significance in my consideration of the problem of the aerobic metabolism of muscle.

There is no doubt that this problem is capable of elucidation in many other and better ways. I have mainly quoted results from fields in which I myself have worked experimentally, and which therefore have played a very special part for me in my deliberations. In my opinion, all the various relations I have submitted to you are conformable, in that they contain no basis for the assumption that the aerobic metabolism of the active muscles is a pure carbohydrate metabolism, indeed, some of them are directly contradictory. It is possible that some of you share the view I have arrived at from this, that the aerobic metabolism of the active muscles is not a pure carbohydrate metabolism, whereas others do not. I scarcely imagine that I have convinced those who do not share my view, but it has been a source of great pleasure to me to have the opportunity of going so deeply into the considerations on which my opinion of the problem is founded.

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# THE CONCEPTION OF CANCER BEFORE AND AFTER JOHANNES MÜLLER\*

HOWARD W HAGGARD

Associate Professor of Applied Physiology Sheffield Scientific School Yale University

IT is becoming increasingly the vogue to commemorate centennials. There is frequently little true sentiment in these gestures, the centennial becomes an excuse for a celebration or for an exploitation. Too often the attitude is not that of reverence for great events of the past, instead, the past becomes only a convenient background against which the presumed progress of the present may be displayed by contrast. I mention this attitude because I venture to bring to you tonight the materials for a medical centennial, and I do not want my object or my attitude mistaken. Neither is in the vogue. I want, if I can, to revive the past and make it live just for a moment in some of the realities it possessed. And my attitude is that of an almost religious obeisance to one of the great men and one of the great events of medicine. Tonight I bring you nothing new but only the hope that in reviewing together here briefly the life of a man we may pause together in our busy ways of the present to revere his memory and to acknowledge a debt.

There have been men—and you can count their number on the fingers of your hands—who have taken up great boulders far beyond the strength of ordinary men and with them have laid down the foundation upon which medicine is erected. Johannes Müller was such a man. The reason that we might celebrate in his honor this particular year of 1938, and the reason for my paper tonight will become evident from a quotation that I read from his works. His words and his sentences as you will see form the foundation for the modern conception of the nature of cancerous growths. In quoting him I pick and choose only a few pertinent sentences from a dozen pages of his book entitled “On the Nature and Structural Characteristics of Cancer and of those Morbid Growths Which may be Confounded with it.” The book was published in 1838.

The first sentence I quote shows with pathetic clarity the lack then

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of any adequate means of differentiating malignant from nonmalignant growths Muller writes "Usually it is regarded as an infallible sign of malignancy if a tumor, after having been extirpated once or twice, returns to the same spot "

As to the need of some better criterion he says "All these circumstances, while they render it extremely easy to confound tumors naturally innocent and dangerous only under certain circumstances, with such as are by nature malignant, afford many additional reasons for seeking some surer means of distinguishing between the two than we at present possess "

He then goes on to say that the classification of morbid growths is wholly deficient, that there is literally none As a first step toward clarifying the confusion he has made a collection of tumors at the Royal Museum of Berlin Of this collection he says

"On close inspection of the preparations, many were met with presenting such peculiarities that it was not possible to assign them any certain place in accordance with the state of knowledge at that time Soon it became evident that if the classification of so many important objects were to have any real value, it would be necessary to devote many years to the examination of them and of other fresh pathological specimens, and to this task the author accordingly betook himself "

Muller next turned to his microscope to utilize the method that he was instrumental in introducing into pathology, he examined under the microscope the tissues in his collection

He says "As early as the year 1836 the author had recognized with the microscope the cellular nature of various morbid growths the cells unless magnified from 400 to 500 times generally look like granules, but on the employment of a high power the cellular structure of most morbid growths becomes apparent "

He goes on further to say that the cellular form in a neoplasm resembles in general features that of the tissue in which the growth occurs And then, and perhaps most important of all, he relates the cellular physiology of neoplasms to that universal for normal tissues He says

"The part which cells sustain in the composition of all morbid growths has recently acquired additional importance from the investigations of Schleiden and Schwann The researches of the former relate to the development of the young cells of plants from nuclei formed in the interior of the parent cells, those of the latter refer to the analogy

between animal and vegetable structures. According to Schwann all tissues in the embryo are formed from cells, which are themselves developed from nuclei, the growth being the result of fresh formations of cells, which afterwards undergo transformation into other tissues. These observations " (and I break my quotation here to mention, what I shall deal with more fully later, that Schwann was the pupil of Muller and made his investigations on the cell in Muller's laboratory and under Muller's inspiration) I continue "These observations led the author to examine morbid growths very carefully. By employing a high magnifying power, cells were observed in malignant growths. The nuclei of the cells were discovered in many instances too, young cells were found. Thus, then, as might have been anticipated, did examination of morbid structures confirm Schwann's observations touching the development and growth of healthy tissues."

The statements which Johannes Muller makes are the beginning of the cellular pathology which his brilliant young pupil Virchow expanded during the next ten years into a basic concept. Johannes Muller in 1838 in unmistakable language—and for the first time—said that cancer is cellular and that the cellular form resembles that of the tissues from which the cancerous growth springs. There in his discovery is the foundation for all modern classification, diagnosis, therapy and research in oncology.

Tonight, using the discovery of Johannes Muller as the dividing point between ancient and modern, I want to outline briefly the conceptions of cancer before and after his work. But mainly I wish to recall to you the man whose discovery we are privileged to celebrate this year.

The external manifestation of neoplasms had, of course, been recognized from early antiquity. The Ebers papyrus gives evidence that the Egyptians knew of tumors, the mention is of a lipoma. Hippocrates wrote of cancers, and used the term *carcinas* for inflammatory swelling and the term *carcinoma* for a neoplasm. Celsus went even further, he recognized clearly visceral forms of cancer and attempted to differentiate clinically malignant from benign neoplasms. Galen observed cancers with considerable accuracy but at once obscured good clinical description with theory, cancers came under his doctrine of the four humors. Cancer was due to the concentration of black bile. This humoral theory persisted until after the discovery of the circulation of the blood and of the lymphatics when Malpighi, Louis and Astruc advanced the idea that

cancers were clotted and degenerated lymph. The dominating view to reach the nineteenth century was that cancer was essentially a general disease, that the growth itself was merely a local manifestation analogous in this respect to the pustule in smallpox. Such was the prevailing view until 1838 when Johannes Muller demonstrated that the cancer consisted of an abnormal growth of abnormal cells.

It is true that before Muller, Bichat had made an important step, he had directed the views of pathologists from organs to tissue or, as he called them, "membranes." Morgagni has said that some organ was always the seat of a disease. The fact that identical symptoms might develop when different organs were affected caused some discord in the harmony of this simple view. It was suggested by Pinel—better known for his work in psychiatry than in pathology—that different organs might have similarities in structure and disease in organs with anatomical similarity though in different parts of the body, might account for this confusion. Bichat took up this idea and carried it further with the conception that organs were built up of basic membranes, tissues which were variously distributed in the organs. Bichat made extensive tests in differentiating the tissues even to tasting them but he did not make microscopic studies. He succeeded in removing the seat of disease from the organ as a whole to its tissues. Pathology became at his hands membranous pathology. It was Muller who first made pathology cellular, and the disease he dealt with was cancer.

And now in approaching the man and his work, I ask you to look back with me for a moment at the situation of his native land, Germany, at the opening of the nineteenth century. Muller was born in 1801. The Germany that he faced was socially and economically the Germany of a little more than a century later—the Germany of 1918. It was post-war Germany, a country in the depths of a depression. It was a hungry, sorry, bitter country, bruised and battered. Like a man shocked by too fierce contact with reality it was prepared to withdraw from reality—to turn to philosophy for escape.

The situation as you will recall developed thus. Near the close of the eighteenth century the last political act of Frederick the Great was the establishment of the League of Princes which brought back a semblance of unity to the Old Empire. In France the trends were in the opposite direction, the Revolution was under way. At first the philosophy of reason interested the educated Germans, but the shift to bloodshed and

the overthrow of the government frightened them and alienated them from the cause of liberty. The French emigrés fled to Germany and took up arms there. France protested, Germany soothed and quieted, the French demanded the abolition of the feudal rights of the German Princes in Alsace, again Germany soothed and quieted. Even the fact that Marie Antoinette was the sister of Emperor Leopold did not bring the Germans into war. At most they concluded a defensive alliance with Prussia, and sent a note of protest to France. The French countered with a declaration of war. That was in 1792, the war ended in 1814. It included the rise of Napoleon and his defeat and domination of the German people. It concluded with the battle of Leipzig and the taking of Paris. The war was over—twenty-two years of war and subjugation. Germany was finally victorious but she was left exhausted facing reconstruction.

There was the war generation, and the dead, there was poverty, debt, actual want. In such situations as these there are reactions, and these reactions are wholly unpredictable. In Germany the reaction came as a wave of idealism, a turn from practical, factual views to romanticism, even mysticism. Why centuries before a similar emotional reaction had taken the form of the dancing mania, why in the twentieth century it takes the form we see today, and why in the nineteenth century it was toward romanticism and the worship of beauty—no one can say, the psychology of such national movements is beyond our knowledge for explanation.

This romantic movement was not an affair alone of poets and imaginative writers, of a cult of beauty that revived interest in the medieval architecture and the learning of the East. It was entered into by physicians and naturalists, men whom, in a more rational environment, we should call scientists. The movement was toward what was called in Germany natural philosophy, a quite different use of the term than that applied in England where natural philosophy was natural science. In medicine the movement took the form of speculation, philosophical considerations and especially the attempts to develop systems that in their completeness would give knowledge in totality.

Now we in medicine today have been educated away from this type of thought. Our emphasis today is continually for novelty—for the discovery of the new as discrete bits of knowledge. I suspect that we err in this direction as far as the romantic natural philosophers of 115 years

alone, as from those whose intellectual foundations have been deeper and wider I do not for a moment doubt this fact, but I do doubt that the conclusions drawn from it can be, as is often attempted, applied to modern pre-medical education. Now it is remarkable but nevertheless a fact that medical educators may interpret matters of science with strict scrutiny and impartial judgment of cause and effect, but sometimes they seem to leave their scientific skepticism behind when they apply their judgment to other fields. With a wholly open mind in the matter I should not be convinced that a humanistic and classical education made Johannes Muller or anyone else a great contributor to medical science. I should wish to be shown that the relation was not wholly one of *post hoc*. Indeed Virchow said that Muller succeeded because he freed himself from the fetters of his early education. One may occasionally wish that the pre-medical education of today might have more science and the medical education less science and more art.

The basic element in the success of Muller is, I suspect, a tremendous intellectual endowment which allowed him to acquire the classics with ease, to read Latin at seven and Greek at ten and not the reading of Latin and Greek at seven and ten that makes his great intellect. We have few Johannes Mullers entering medical school today and there is always danger in attempts at emulation unless the emulator has the intellectual capacity of the man whose educational system he attempts to emulate. The physicians of the time of Molière were highly educated in the classics and in the humanities but that advantage, if it were an advantage, did not compensate for, rather it exaggerated, the deficiencies of a poor medical education. In this digression I merely stated my skepticism as to whether the classical and humanistic education of Johannes Muller was a determining influence toward his later medical productivity. There were many other physicians in Germany educated as well as he was and they did not reform German medicine, they merely devoted their efforts and their education toward the development of humanistically tenable but wholly unscientific systems. I believe that Johannes Muller was a man of superlative intellect and of a personality especially suited to the line of his career. And finally, I think he had opportunity and also some of that nebulous element called luck. Johannes Muller did not spring from the classics fully armed with the medical genius he displayed in later years. He had, as you will see, his difficulties to overcome and his adjustments to make and he did not always make them easily.

He was, as I have said, destined for the priesthood, but at about the age of sixteen he read with great enthusiasm the scientific writings of Goethe. The suggestion there was away from abstract thought and toward concrete factual nature, it was away from natural philosophy in which he had been steeped and toward the natural science of which he then knew so little. I have said that opportunity as well as intellect and personality are necessary for the display of greatness. Without Goethe's influence, Germany might have had a good priest in Johannes Muller and medicine might have lost one.

But whatever the forces were that changed the channel of his career we find him, at the age of eighteen, enrolled as a medical student at Bonn. There he was exposed to two great but opposing forces, one was the philosophy of Schelling toward which he was drawn both by his early education and by a strain of mysticism deep in his own make-up. It was this indefinable spiritual quality which I call here a strain of mysticism that perhaps later inspired his pupils and bound them to him as Virchow says in close ties as if by a religious bond. The other influence, the opposing force that drew him away from philosophy, from theorization and dreamy speculation was, strange to say, anatomy. Anatomy was a factual, realistic subject, the very antithesis of natural philosophy. In the struggle between these two forces, anatomy won out, it aroused his youthful naiveté to the extravagant exclamation that indicates his capitulation: "What does not come under the knife counts for nothing!" It was the extension of this view into the medical education of the nineteenth and early twentieth centuries in this country that made so painful for most of us here the first year of medical school.

Muller in his fourth year of medical education—1823—wrote a prize essay on the respiration of the fetus. Later Virchow, commenting on it, says that it was a work remarkable for the extent of the knowledge shown and for the ingenuity of the experiments carried out.

Having obtained his degree at Bonn, he went to Berlin to take his state examinations and there met, and for a short time worked with the physiologist, Rudolphi. Rudolphi held natural philosophy in contempt, he struck a responsive note in young Muller with his statement that anatomy was the foundation of medicine. Johannes, then twenty-two, was deeply influenced by the skepticism, the worldliness of this older man, and Rudolphi in turn, recognizing the merits of the youth—recognizing too, and perhaps pleased at his own influence upon the keen if still



naive mind, gave the boy an English microscope. The microscope was to play a determining factor in Muller's subsequent career.

The need to earn a living took young Dr. Muller back to Bonn where he made a rather meager livelihood from teaching and from a small practice, occasionally he was assisted by his mother. The death from peritonitis of a friend under his medical care convinced him that the practice of medicine was not to his liking, he dropped it and spent his time on his studies and teaching. These years, one may judge, were trying ones for Muller, a period of adjustments which he did not make easily. In the midst of it, at the age of twenty-five, he married Anna Zeiler, daughter of a landowner near Bonn.

In a poem which he wrote to her he promised her an immortal name in lieu of more material dowry. And then in the frantic burst of scientific research to gain that immortality, his health gave way. I do not know what his trouble was, a breakdown of a nervous nature his commentators say, and one cannot help but assume that these were days of frustration and perhaps unhappiness for a brilliant intellect, a driving ambition—a man torn between mysticism and the study of anatomy, newly married, poor, discontented with medical practice and without the scientific recognition he craved. And all this, be it noted, in an environment where the premium for intellectual endeavor was put on speculative flight of fancy. He did not break seriously under the strain, his health recovered and he returned to his researches. It was in this period that he did his work on the embryology of the generative system remembered in the duct of Muller, it was then also that he carried out his investigations on the nervous system and the sense organs and published his comparative physiology of vision. In that book he confirmed and established Bell's doctrine of spinal nerve fibers. All this and more were completed before he was thirty-two years old.

It was then that Rudolph died and Muller was called to take his place in the chair of anatomy, physiology, and pathology at Berlin. The following year Muller published the first volume of his *Manual of Human Physiology* which was, as I have said, to exercise a determining influence in turning the German medical mind away from natural philosophy and toward science. It was to bring brilliant pupils to Muller's laboratory at Berlin.

It is of Muller as a pathologist that I speak particularly tonight. And in that field his important contribution to his students was his insistence

upon the use of the microscope in pathological study. This was a procedure virtually new in pathology and certainly unique as a routine. It was method that he urged upon his students, method of approaching problems and method of solving problems. Those methods must have become almost a primary way of thinking in the men who passed through his hands. They thought in the manner of quantitative evaluations sometimes in little matters as well as large. Thus when DuBois-Reymond wished to tell of the industry of his teacher, what was more natural than that he should use not adjectives but figures. He computed Muller's average literary output for thirty-seven years as amounting to thirty-five printed pages and 83 published plates drawn by his own hand each seven weeks.

I have mentioned the names of some of the more important students who were drawn to Muller and inspired by him. Best known of course was the aggressive Virchow, but for the discovery of Muller with which I deal tonight the most important was Theodore Schwann. It was Muller's insistence upon the use of the microscope that led Schwann in Muller's laboratory to discover the animal cell and postulate the cellular theory of tissue structure. It was this discovery which was not published in full by Schwann until 1839 that opened the way for Muller's discovery that cancerous growths were cellular, it also laid out the careers for two of Muller's most promising pupils. Henle, the histologist and anatomist, and, of course, Virchow.

So basic is Schwann's postulation to Muller's discovery that I digress for a moment to trace the outline of its development.

The original conception of a cellular structure is entirely from the botanists. In the seventeenth century Robert Hooke, using a magnifying glass, had noticed the "small boxes or bladders of air in cork." A more detailed structure of plant cells could not be investigated until the compound microscope was developed. It was 1833, the same year that Muller went to Berlin, that the botanist Robert Brown discovered the nucleus in the plant cell. In 1836 (although published in 1838) Schleiden proved that plant tissue is made up of cells and developed only from the multiplication of cells. Muller's amiable and phlegmatic pupil Schwann had seen nucleated cells in animal tissue. Influenced by Schleiden's work he searched for cells in all the tissues he knew of. He found them and from his findings formulated the basic law of morphology for all vegetable and animal tissue. To quote his words: "There is one universal principle of

development for the elementary parts of organisms, however different and that principle is the formation of the cells"

One can almost sense the excitement that must have pervaded the laboratory of Johannes Muller in those years of 1836, 1837 and 1838. Remember that this was before Virchow came there as a student, he was to make the greatest advances with cellular pathology and to obtain the greatest recognition but the fundamental discoveries were made before he came to the laboratory in 1839.

I have already read from the works of Muller how he was led to turn his microscope on cancerous growths and to see the cancer cell and see further that it took the general shape of the cells of tissue from which it sprang.

For my purposes here this basic discovery made public in the year 1838 is as far as I wish to go with the work of Muller. He died, as you know, at the age of fifty-seven, probably of an arteriosclerotic accident, for he was found dead in the bed to which he had retired in good health.

There is just one more quotation from Muller that I make before I leave him. Muller was not infallible but he was sometimes dogmatic. Thus on one occasion he said that the rate of transmission of the impulse in the nerve fiber would never be measured, within a decade his pupil Helmholtz had measured the rate. And again—and this is the quotation pertinent here—when he had finished his work on the histological classification of cancers he wrote in his book these words:

"Microscope and chemical analysis can never become a means of surgical diagnosis for malignant growths, it were ridiculous to desire it, or to suppose it practicable."

Now if there is any one thing in which microscopic examination of neoplasms has been useful, practicable, it is diagnosis.

The enormous volumes of microscopic anatomy of neoplasms are at once a refutation and also a little justification of Muller's dogmatization. The morphological studies for classification go on endlessly with a descriptive refinement that forces one to the conclusion that while the microscope shows the cancer cell, this cell itself has no fixed morphology, only approximate. If one may hazard here a dogmatization with all dangers of dogmatization it is that cancer morphology has not and will not contribute toward the really fundamental discovery sought today—the reason for the cancer cell—cancer causation. The search today still centers on the cell but not its shape, rather its physiology, not cellular

morphology, but cellular reaction

Johannes Muller's statement that cancer is cellular has remained since his day the foundation of all cancer research. Literally everything we know about cancer, except its gross appearance, has been gained in the single century that has passed since his publication of 1838.

Cancer causation was from the beginning and is today the great riddle. And such knowledge as we have gained and are gaining makes each year more dubious the possibility of any completely successful method of treating the developed cancer. I do not mean in any way to belittle the achievements of the therapists or to imply that the wider and fuller application of their measures would not save many lives. It would. But everyone in medicine knows that the often quoted slogan of early detection and cure has elements of well intended sophistry. They know, too, that no new successful principle of treatment has been developed since the time of Hippocrates. In his day there were surgery and caustic plasters, in our day there is better surgery while radium and x-ray have replaced the caustic. The aim then was, and the aim now is, to remove or destroy the neoplasm. The principle is unchanged. We all see, I think, that success must lie in other directions. And the essential to that success must be the discovery of cancer causation. Occasionally specific therapy is discovered accidentally before the cause of the disease is known. But such is rare. Usually the discovery of the cause must precede the development of treatment or prevention.

The scientists of Muller's day saw that fact and they gave us hypothesis, there was Virchow's chronic irritation theory, Cohnheim's stimulation of misplaced embryonic rests with Ribbert's later modification, there was the heredity and there was the parasitic theory.

The experimental scientific investigations that have given promise of the eventual solution of cancer causation showed first the autonomy of the cancer cell. Hanau, as early as 1889, made successful transplants of cancer cells in rats, his work was confirmed in 1901 by Loeb and in 1903 by Jensen. It was carried to its logical conclusion by the *in vitro* growth of cancer cells by the method of Harrison.

Next in these few and broad steps I take in reviewing cancer study was the experimental production of cancer. This new era in cancer research started with Fibiger's discovery of the cancer in the stomach of the rat caused by a nematode carried by the cockroach—in itself one of the most exciting stories in modern scientific research. Fibiger's work

stimulated interest and efforts to produce experimental cancers and next came the tar cancers in the ears of rabbits

It is a long jump from there to the discovery in tar of the carcinogenic penathrene ring, and the discovery of this ring in normal secretions of the body and in vitamins It is a long jump too from simple tar cancer to the virus cancer of Rous and still another to the isolation of at least one virus as a non-living chemical substance Today cancer research moves from the microscope to the test tube, from morphology to chemistry And the promise held today for the discovery of cancer causation and for the subsequent relief from the scourge of cancer grows brighter

The great danger to the search for the solution of the cancer problem is not ignorance, not lack of means of approach, not failure of science, it threatens always from another direction It is the danger that some social cataclysm shall shake the rock of science and dislodge the scientist It is then that men's minds lose the desire for facts, for realities, they turn to the consolation of philosophies, they turn to bizarre social manifestations This has happened in the past, it may well happen again Science, as we know it, is a solid structure but the scientist who builds upon it is a man and as a man is at the mercy of his social environment That is the frail structure and the scientist is no stronger than its strength German thought of a century ago rose as I have traced from speculation to productive science, within our time it fell again These things are not of one country, or of one race, or of one century They are universal and eternal And so I say again, barring the social cataclysm that will dislodge the scientist, the way is clear and open to the discovery of cancer causation

Perhaps in this building or its successor a hundred years from tonight there may be again, with the problem of cancer then solved, the suggestion that the memory of Johannes Muller, who defined the problem for its solution, be revered You and I will not be here But I hope that he who is privileged to recall the memory of that occasion will recall the man as he is recalled in the words of his pupil Virchow They are almost a prayer in the rise of science above social retardation He said "The cult which he served as a priest of nature bound his pupils to him in close ties, as if by a religious bond, and the serious priestly fashion of his speech and movements compelled the veneration with which everyone regarded him His mouth, with its tightly compressed lips, conveyed a notion of severity, around eyes and forehead played an expres-

sion of profound thought, every furrow in his face stimulated the idea of a perfectly finished work—thus did the man stand before the altar of nature, freed by his own energies from the fetters of education and traditions, a living witness to personal independence!”

## EMOTIONAL FACTORS IN HYPERTENSION\*

KARL A. MENNINGER

The Menninger Clinic, Topeka

As I consider the elaborate and thorough-going discussion of renal medicine which has been prepared by your committee for this Graduate Fortnight, I am appalled at the responsibility which devolves upon me as almost the lone contributor to a consideration of the psychological factors in disease. That this aspect of the symptom of hypertension or of the diseases in which it occurs should have been included on the program, even this once, may be taken as an indication of the change in medical attitude since those days when a reference to psychology was tantamount to a reference to spiritualism or necromancy. If, on the other hand, one brief hour out of hundreds devoted to this point of view seems disproportionately small, it may be charged in part to a lingering reluctance to consider psychology a definite science, and, in part, to the far greater precision of the microscope and the test tube as compared to our measurements and estimates of human behavior and emotion.

Since I have so large a subject to present in so short a time I cannot now analyze further our resistances to psychological concepts in medicine or refute the impression that the scientific method cannot be and has not been applied in psychology as in physiology and chemistry. I shall indicate first the point of view which I think probably correlates the psychological, physical, and chemical findings in disease, then I shall present some of the psychological data which have been accumulated concerning the subject of hypertension, abbreviating the physical and chemical aspects which have been so excellently presented in previous lectures here, I shall indicate some of the practical difficulties in arriving at more definite and exact conclusions than we can offer at the present time, and, finally, I shall submit a few practical suggestions.

*Point of View* I truly believe that the word *psychogenic* has done more to confuse the issue of the emotional factors in disease than to clarify it. Psychogenic as applied to an illness implies that the disease arises

\* Delivered November 5, 1937, in the Tenth Annual Graduate Fortnight.

some way or other in the patient's mind and, with the persistent medieval concept of mind which prevails not only in medical thinking but elsewhere, this is equivalent to saying that some diseases are consciously or unconsciously conjured up out of "mind-stuff" and deposited upon a surprised and unwilling body which functions according to physical and chemical laws independent of psychological laws. As one intensely interested in studying the emotional factors in disease, and one who has proposed numerous postulations concerning the contributions of these factors to disease, I should like to make the bald statement that I do not believe that any disease is psychogenic.

Such a one-sided attitude is no better than that held by the clinician who totally ignores the psychological factors in disease and thinks of disease solely in terms of physics and chemistry. For I do not believe, either, that any disease can be accurately described as physiogenic or chemogenic. Physics overlaps chemistry and both overlap psychology, but the laws of one are not the laws of the other in our present state of knowledge. The time may come when we may describe in a single mathematical language a stone in the kidney, an antitoxin in the blood stream, and the reactions of a child who sees his mother strangled. But at the present time we scientists must profit by the example of Aesop's six blind men and the passing elephant. We must each lay our hands upon it from the vantage point that is ours and, by comparing results and trying out hypotheses to explain the discrepancies in our observations, instead of contradicting and ignoring one another's data, we may avoid the ignominious errors of the six blind philosophers.

My feeling is that as a result of traditional medical education, most patients are examined physically and chemically but not psychologically. We would call a man a quack who treated a case of appendicitis after making a psychological examination but no physical examination, why should we condone the treatment of a case of anxiety hysteria after a physical, but no psychological examination? If we truly subscribe to the theory that in every disease the proper investigation would uncover psychological as well as physical and chemical features, we must believe in the existence of a special psychology for every disease. Perhaps the medical textbook of the future will systematically supply these. For the present we must content ourselves with a much better knowledge of the psychology of certain kinds of indigestion, for example, and even of gastric ulcer, than of the psychology of chronic nephritis or carcinoma.



And now for the psychology of hypertension

Hypertension is, of course, not a disease but a physical condition which is easily ascertainable and measurable. Parenthetically, I have often wondered if the introduction of the sphygmomanometer has not killed more patients than it has saved. In our search for definiteness in biological science, it is difficult to remember that precision in measurement is not equivalent to accuracy in interpretation. The feeling of security which followed the introduction of this ingenious device of Riva-Rocci and von Basch led us astray and numbers became more important than meaning. Many a doctor has frightened his patients to bed if not to death with an ominous and incorrect interpretation of the incontrovertible figures of the dial or mercury column.

But hypertension is a condition in which not only the physical but also the psychological factors are readily recognizable, although the latter are not so easily measurable. The parallelism of blood pressure fluctuations and emotional fluctuations was one of the early physiological correlations.\*

Of course we have learned a good deal about blood pressure since those earlier days.\*\* We—or some of us—have ceased to look so assiduously for a “cause” of hypertension and have sought rather to understand its total significance. From the physiological and anatomical standpoint, we are quite generally agreed that it is due to vasoconstriction and that the vasoconstriction is due to sympathetic stimulation and parasympathetic inhibition. That these effects accompany or are accompanied by emotion is also generally accepted.

\* The influence of the theories which embodied the organic explanation for the increase in peripheral resistance in primary hypertension has not as yet been erased. For this the term hypertension itself is largely to blame in that it implies a static phenomenon. The lability of the blood pressure, first recognized by Gumprecht<sup>1</sup> emphasized by Mosenthal and Short<sup>2</sup> and reiterated by Asman<sup>3</sup> is the most singular characteristic of essential hypertension and is not sufficiently appreciated. These striking fluctuations of the blood pressure imply a morbid physiology, only the sequelae of which can be anatomical. In the opinion of Kilin<sup>4</sup> this lability of the blood pressure is explainable only on the basis of a vasomotor disturbance which is in accord with the view of Norris and his associates<sup>5</sup>, who state that the vasomotor mechanism in patients with essential hypertension is sensitized and that hypertension in those instances is simply an exaggeration of a normal physiological blood pressure response. These contentions are substantiated by the findings of Mueller and Brown<sup>6</sup>, that the diurnal and nocturnal fluctuations in blood pressure in normal individuals and in patients with essential hypertension differ only in degree and that patients with essential hypertension show extreme reactions to stimuli which in normal persons would cause only mild reactions. That is to say the blood pressure responses to emotional stimulation in the hypertensive and in the normal individual are qualitatively the same, the difference being only from a quantitative standpoint. That the ordinary and usual incidents of life provide stimuli sufficient to cause marked fluctuations in the blood pressures of patients with essential hypertension has been demonstrated by Brown, O'Hare<sup>7</sup> and Mosenthal and Short.<sup>8</sup>

\*\* To the older writers of course hypertension was primarily a disease of the blood vessels of the kidneys which in some toxic or mechanical way affected the rest of the vascular tree, when this theory was exploded by further clinical studies the blame was put upon the suprarenals. Later guanidine, cholesterol, peptone like substances, the potassium calcium ratio, to say nothing of alcohol, tobacco, hypoelectricity of the carotid sinus and numerous other agents were incriminated, one after another of which has been disproved as the fundamental etiologic basis of arteriolar hypertension.<sup>9</sup>

Whether the emotion is a cause or an effect of the hypertension still seems to puzzle many writers. On the one hand, many physiochemical researches proceed as if the emotional reactions were by-products. On the other, many practical procedures such as the lie detector\* proceed upon the assumption that emotional disturbances can cause blood pressure fluctuations.

At this point may I refer again to the elephant and the six blind men. I see no reason why we should feel it necessary to seek for first causes when our daily experience, if not logic and philosophy, convince us that none such exists! What impresses some physicians who palpate the elephant is the fact that they find certain definite, characteristic, structural and chemical pathology in advanced and fatal cases of hypertension. What impresses those who have made psychological examinations of the same elephant is three-fold:

- (1) The fact that transient hypertension may be induced in persons by emotional stimulation
- (2) The fact that some of these cases show gross abnormality of emotional status or reactions
- (3) The fact that chronic hypertension may sometimes be reduced by various procedures essentially psychological in nature

Without attempting to solve the riddle, which may be, after all, like the riddle of the priority of the chicken or the egg, I propose to devote my remaining time to an examination of these three sources of psychological data.

## 1. TRANSIENT HYPERTENSION IN NORMAL PERSONS

I have already discussed this briefly. The only point I would add here is an echo of what is now becoming increasingly familiar to all investigators, namely, that we do not know very definitely what a normal blood pressure curve looks like, since single readings are almost meaningless and continuous readings almost impossible to obtain. Hence hypertension is a relative term of great inexactness. I have seen the systolic blood pressure of a patient who was being examined by an assistant mount

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\* The theory upon which the deception test is based was suggested as far back as 1600. Hugo Muensterberg of Harvard suggested the use of an instrument for recording blood pressure, pulse and respiration for the detection of guilt in 1907, and Marston in 1914 experimented with a blood pressure technique for detecting deception. Larson<sup>10</sup> <sup>11</sup> continued the work under direction of Chief of Police August Vollmer in Berkeley, California, and succeeded in establishing a successful technique. Keeler<sup>12</sup> designed an instrument for recording simultaneously the blood pressure and respiration over a period of time which is widely used today. (See also Inbau<sup>14</sup>.)

fifty millimeters of mercury merely as a result of my entrance into the room. We have no way of knowing how much it may have mounted previous thereto as a result of my assistant entering the room or as a result of applying the cuff. The practical utility of the lie detector has been proved, but what we do not know is how much the anticipation of applying the lie detector may have affected the arterial tension in the first place. Of course this does not invalidate the test. I simply mention it to show that until we are able to take a patient's blood pressure without his knowing that we are taking it, we have no way of knowing what it *was*. We do know<sup>15</sup> that the blood pressure of a person with what we call normal vasomotor stability usually rises with certain emotional states, which may be experimentally stimulated, and returns rather promptly to a lower point. To explain a systematic elevation of blood pressure it would be necessary to assume a continuous series of such stimuli. This, of course, is one deductive theory offered to explain the relation of the emotional pathology found in actual cases of hypertension to that hypertension. We shall look next at some of these cases in which this continuous or chronic emotional pathology has been found.

## 2. EMOTIONAL PATHOLOGY IN HYPERTENSION

We psychiatrists sometimes reproach internists for their apparent disinclination to seek for the psychological data which might be related to the continuous autonomic stimulation which results in the continuous splanchnic constrictions which result in the hypertension. I want to withdraw all my reproaches, because I can testify from personal experience that collecting data regarding the emotional factors in hypertension is for many reasons an exceedingly difficult task.

For one thing, one must distinguish between conscious and unconscious emotional factors. It is hard enough to uncover the conscious emotional pathology of a patient and to evaluate its strength, its effect upon his total personality and his vascular tension, in particular. It can be done, usually, if one has the patience to listen to what the patient has to say. But it is still harder to get at the unconscious emotional factors, those which the patient cannot tell us about even if he would. This requires the psychoanalytic technique, and, therefore, a great amount of time.

It is very hard, too, to separate the emotional factors stimulated by the physician himself and by the whole program of examination and

treatment from those more continuously operative. Again, even when one discovers and evaluates the emotional factors in a particular case quite definitely, it is exceedingly difficult to show except by deductive hypothesis just how or how much these things affect the blood pressure. It is impossibly absurd, for example, for a psychoanalyst who is listening quietly to a patient who, with sobs and tears, is confessing some poignant source of anxiety, to interrupt this by leaping from his chair to seize and apply a sphygmomanometer. Or consider this complication. I was conversing with a patient with very severe hypertension while an assistant took blood pressure readings regularly every two minutes. The patient had voluntarily renounced smoking after many years of heavy addiction. I proposed that we observe the effects of smoking a cigarette and he willingly cooperated. My assistant redoubled his efforts to make accurate consecutive readings. While we were waiting for the cigarette "to take effect", my patient suddenly remembered a distressing occurrence which had taken place in his home the previous week and began to relate it in detail. His systolic blood pressure rose thirty millimeters of mercury but whether from the cigarette or from the recollection, who can say?

Nevertheless, in spite of all these difficulties some definite psychological studies have been made both of the conscious and of the unconscious emotional factors in hypertension and some fairly definite tentative conclusions arrived at. In the brief time at my disposal I can only summarize these conclusions. Wolfe<sup>16</sup>, Dunbar<sup>17,18</sup>, Hill<sup>19</sup>, Stevens<sup>20</sup>, Alexander<sup>21</sup>, Moschowitz<sup>22</sup> and others have reported such studies. The findings correspond fairly well. They indicate that patients with hypertension are characterized by an external poise, often gentleness and amiability, be-

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\* For example, Wolfe<sup>16</sup> studied hypertension cases in the medical department of the Columbia Medical Center. He believes that the development of hypertension is the result of repressed (i.e. unconscious) emotional factors chiefly aggressions, hatred and guilt feelings.

To what extent this situation is specific we are not ready to say. It seems noteworthy, however, that successful handling of this factor alone surprisingly often leads to improvement or even symptomatic cure although the fundamental neurosis may not have been adequately treated. He cites a case of a single man of 25 admitted to the hospital for hypertension, his blood pressure being in the neighborhood of 160/90. He also had some fears of fainting and was found also to have deep but largely repressed resentment and hate. His dreams for example were of a predominantly sadistic masochistic character. After three months or superficial psychotherapeutic treatment emphasizing relaxation his blood pressure was reduced to 126/88.

Dunbar<sup>18</sup> working in the same clinic reports among others a case of hypertension in a married woman of 39. Her blood pressure on admission was 190/100 and was said to have been higher previously. A careful psychiatric study showed that there was much reason for the existence of great resentment, anxiety and hostility and when these tendencies were to some degree brought to consciousness and related to her symptoms she showed a marked improvement in her external adjustments and coincidentally a drop in her blood pressure to an average of 130/90. This was accomplished in a few months which is rather extraordinary in view of the fact that she had been an invalid on account of such symptoms for the preceding eighteen years.

neath which there exists a strong undercurrent of fear which arises from the existence of strongly repressed aggressions, usually dependent upon resentment over threats to the patient's dependent security. To re-phrase this rather condensed statement by a paradigm, I would say that hypertension might be expected in a patient whose early childhood was threatened by poverty, death or other disaster whereby he was forced into a premature self-reliance which later shows itself in the form of more or less external (material) success, but accompanied by a constant internal anxiety set up by actual or imagined threats to his security. Upon examination such patients completely deny or reject all suspicion of resentment, hate or fear but describe situations in which such emotions could not but be stimulated. Continued study of such patients often evokes, suddenly and sometimes to the patient's great surprise, frank avowal of such feelings, and then, the real (i.e., the original) reasons for them.

I remember, for example, a dramatic experience with a patient, an author, who came to us because of the sudden loss, two years previously, of her ability to write. It was discovered incidentally that her systolic blood pressure readings were continuously over 200 mm. of mercury. After a few introductory sessions in my office during which she was pleasantly, but irrelevantly, communicative, she suddenly asked for paper and pencil, ceased talking and began writing automatically. The handwriting was not her own and the communications were signed by a strange name. She had never done this before. She dashed off hundreds of pages in this way during the next few weeks. She was amazed at what she wrote since it concerned herself, intimately, and while she was able to confirm its truth after she had written it, she insisted that she had known nothing about it prior to the automatic writing. Among other things she confessed frank wishes to kill her mother for reasons, also given, which seemed at least partially to justify such wishes. She ultimately regained her ability to write professionally and her hypertension diminished.

A more characteristic example is that of an old maid who for thirty years had been the trusted private secretary of the executive head of a large business. Apparently he had supreme confidence in her and was absent from his office weeks and even months at a time. Much as she appreciated this confidence, however, and great as her admiration and respect for her employer were, she was exceedingly distressed by the growing rebellion of factions in the business which threatened to over-

allow his control of it, and, incidentally, remove her from her position. When she would appeal to him to return and assume the responsibility of controlling the business, he would reply that he had confidence that she would do the right thing. This she felt totally unequal to, but never one word of criticism or reproach of her employer would pass her lips even in the intimacies of a professional consultation. This depression and psychic tension were associated with a high degree of arterial hypertension.

In this connection it may be fitting to say that in several cases in which I have made blood pressure readings in connection with psychoanalytic treatment I have observed a temporary increase in blood pressure for several months toward the end of the analysis, corresponding with the resentment and fear experienced by the patient over the contemplation of being extruded from the protective care (as he envisages it) of the physician. Of course an analysis is incomplete if this fear and concomitant hypertension have not receded as the patient takes a more realistic view of the situation and increasingly utilizes his capacity for directing his hostilities into useful channels, thereby also reducing his feeling of helplessness.

The objection may be made that cases of hypertension studied by psychiatrists are exceptional in nature and hence not suitable material from which to draw general conclusions about hypertension. Without conceding this to be a valid objection, I personally undertook, as have some other psychiatrists<sup>16 17</sup>, to make psychological studies of patients, referred, by cooperating internists, for this purpose only. My purpose was to see if a week's intensive study would lead to any inferences as to the *probable* nature of the unconscious material, and to any practical conclusions as to the significance or potency of the conscious emotional factors. I had in mind the opportunities and necessities of the average general practitioner or internist to whom we psychiatrists are constantly commending the desirability of searching for and dealing with the emotional factor in disease. What could a doctor who was trying to do this see in carefully studied cases of hypertension, and what further could one with psychoanalytic experience justifiably infer or suspect?

An illustrative case can be mentioned briefly. A married woman of fifty-one, with a blood pressure averaging 183/104 and occasionally much higher, had a fairly characteristic psychological picture. She was an exceedingly gracious and dignified, composed person, amiable at all times

under the varied experiences of a complete psychiatric examination. For ten years she had been the executive head of a large international organization and had traveled extensively in Europe, Asia and all parts of this country making addresses at large and small meetings. She was married to a physician twenty years her senior. Two years prior to the discovery of her hypertension he had been removed from a position which he had held for many years and was attempting to make a living for his wife and himself by the re-establishment of a private practice. Progressive loss of vision made this still more difficult. The frequent public appearances which his wife was obliged to make in connection with her work required an expenditure for clothes at a time when it was even difficult to buy sufficient food. This financial restriction in conjunction with her pride and the necessity for making a good appearance before her townspeople and her organization was an increasing source of conscious anxiety to her as was also the increasing age and anticipated helplessness of her husband. As she was discussing this latter point her systolic blood pressure mounted to 238 millimeters. Consciously, of course, it would have been absurd for her to blame her husband for their predicament but the unconscious is not guided by any such rules of justice or fair-mindedness. Hence her hostility was repressed, the inner psychological tension paralleled the high arterial tension.

### 3 THERAPEUTIC EFFECT OF PSYCHOLOGICAL TECHNIQUES IN HYPERTENSION

In referring to the work of various authorities with hypertension cases, I have not mentioned the frequent reports of cases benefited by psychotherapy, the third fact which impresses the psychologically minded observer. Some of these are very striking, Hill<sup>19</sup> for example, reported a case of a man of thirty-two who for fourteen years had been known to have hypertension. This patient was under treatment by psychoanalysis and following one particular day's treatment, the details of which have been completely reported by Hill, his blood pressure fell from an average of 180/120 to 145/90 and thereafter never exceeded 135/90 and was frequently read as low as 125/85. No other treatment was administered and there was no change in his habits of living. I myself have reported a few cases<sup>23</sup> and I have already referred to the fact that frequently patients show a rise and then a fall in blood pressure near the termination of an

analysis This observation has been confirmed by an ingenious piece of clinical research reported by an internist, David Ayman<sup>24</sup> of Boston Ayman was impressed by the widely varying reports of the successful treatment of essential hypertension by many different drugs and methods He carefully analyzed thirty-five research projects of this type and discovered that in practically every article complete or partial symptomatic relief was reported in spite of the enormous range of treatment methods He noted, also, that complete failure was seldom reported He concluded that there must be some common factor associated with the administration of these various treatments which was not recognized by the experimenters, and as a research project studied the effect of the administration of a placebo (dilute hydrochloric acid) As minimal criteria of a diagnosis of essential hypertension he insisted that the patient should have had at least five abnormally high readings of blood pressure and that they should have been observed for at least two months prior to the beginning of treatment An otherwise unselected group of forty patients was then treated and followed Thirty-three of the forty patients showed definite improvement, i e., the treatment was 82 per cent successful The symptoms were relieved and the blood pressure fell, however, with a considerable disparity in the parallelism of the two factors

Ayman was convinced that the common element in the treatment to which the patients responded with so much benefit was that of "the enthusiastic giving or doing something for the patient" His point is that *treatment*, regardless of its nature, benefits the hypertensive patient Not being a psychoanalyst or psychiatrist, he does not interpret this in terms of the transference effect with which we are so familiar, but makes it clear that the patient feels better because he is now under the protective observation of an individual of authority who takes an interest in him

How closely this corresponds to the psychoanalytic findings already reported scarcely needs elaboration If even the placebo of dilute hydrochloric acid used by Ayman is sufficient to give 82 per cent of success in treatment of the symptoms with an unrecorded percentage of success in the reduction of the blood pressure itself, one must assume that some emotional experience takes place which lessens the symptoms and the tension and presumably this is brought about by a lessening of some inner



tension which the patient unconsciously maintains \*

These are the aspects of the elephant that impress the psychologically minded. How they are to be correlated ultimately with the physical and chemical findings, I do not know. There is a theory that would adequately reconcile some of the discrepancies in our viewpoints. Let us think of the physical observations in regard to hypertension as one aspect of the disease and let us think of the chemical observations that have been made regarding it as another aspect and let us think of the psychological observations as still another aspect. Let us refrain from assuming that any one of these is responsible for the others. In other words, let us not attempt to explain the irritability of the hypertension patient as *due to* his tension, and let us not explain the hypertension as *due to* guanidine or disturbance of the potassium-calcium ratio or anything of this kind, let us not explain the kidney changes as *due to* the arteriosclerosis or vice versa. In these fields let the descriptions stand by themselves and let us look for something back of all of these observations which may be regarded as a coordinating determinant. This, I think, is the value of the concept of *primary constructive and destructive tendencies* with which we are familiar in metabolism, the phenomenon of inflammation, the chemical process of ionization and similarly in the field of behavior. Lack of knowledge precludes our finding very apt words to describe it and perhaps Freud's choice of the expressions "life instinct" and "death instinct" was not the most fortunate one. But certainly the idea of two opposed but interacting forces, one in the direction of life and creativeness, and one in the direction of death and destruction, manifesting themselves in physical, chemical and psychological phenomena, lends itself in a very fruitful way to our problem. What we call physiological and chemical and psychological observations are all interrelated mechanisms resulting from instinctive drives originating deep in the structure of the personality.

\* We might here examine the thesis set forth by some of the more progressive internists (see Allen<sup>12</sup> et al) to the effect that hypertension probably arises upon a 'constitutional' i.e., hereditary, basis which is designated as the specific factor and to which some non specific factors, toxic, psychic or mechanical are added to produce the final result. There is very good evidence for this view, particularly the frequent occurrence of hypertension in certain families, the evidences of predisposition to hypertension in certain individuals who show the vasomotor hypersensitivity indicated by the Hines Brown Test.<sup>13</sup> On the other hand it is well known that Negroes and Chinese do not in their native countries develop hypertension. It is also well known that people of these same races do develop hypertension in the United States or under other circumstances of occidental culture. This fact is rather devastating to the constitutional or specific theory. It is on the other hand, entirely understandable from the standpoint of the psychogenic theory. This will require some explanation because one's first thought is that certainly the Chinese in China and the Negroes in Africa have plenty of occasion for fear in those countries perhaps even more so than in this country. But there is one source of fear from which the Chinese and Africans do not suffer under the domain of their native civilization which they do experience in ours and this is the anxiety arising from the strong super ego development which the occidental civilization induces.

## PRACTICAL SUGGESTIONS

Whether this theory is correct or not, it has at least two pragmatic evidences of validity

In the first place, it has been definitely demonstrated that a passive conversational approach to a patient often enables the release of some resentment (and hence of the necessity of some repression, and of some fear) and this decrease in psychic tension should be reflected in a decrease of vascular tension. Whether clinicians agree with the explanation or not, there is general agreement in the literature as to the observation and, and therefore, as to the therapeutic validity of this method of treatment, a method which, nevertheless, is shockingly neglected. To put it in plain English, physicians may definitely relieve hypertension by giving the patient a quiet, non-critical, sympathetic audience. All reference to the degree of hypertension, its potential dangers, its complications, is omitted from the conversation. The effect is not one of suggestion, it perhaps needs to be said that for such patients encouragement about the reduction of blood pressure is not necessarily good therapy, in his unconscious, each patient needs his symptoms and to encourage him to think that these symptoms are disappearing without a perceptible reason may undo the good done.

Another practical suggestion. There is much reason to believe<sup>26 27</sup> that self-directed aggressions can be turned outward by the authority of the physician and if our theory has validity, any extroversion of the aggressions which is not mechanically too strenuous should be of benefit to the patient. In other words, instead of forbidding exercise to a hypertension patient, it should often be recommended, instead of prohibiting work, it should be insisted upon. I am confident that the death of some hypertensive patients is hastened by physicians who remove from them the only available or acceptable forms of aggression to which they have had access, i.e., golf, walking, or hard work at the office. Many internists know this intuitively and I have heard them cavil at those colleagues who still preserve a childlike faith in the so-called "rest cures." My own clinical experience with hypertension is not sufficient to know how generally correct or incorrect it is but certainly the psychological theory is all on the side of those who advocate *mild*\* exercise and continued work and regard the forbidding of these things as the greater hazard.

\* Of course one can overtax long weakened vessels

## CONCLUSIONS

No one man can see enough patients representing any one syndrome to draw any final conclusions about it. When I consider the millions of patients who exhibit the symptom hypertension and compare those with the paltry few that I myself have observed or even the few thousands that I and all my colleagues together have seen, and examined psychologically, I realize that we must rely upon deductive theory rather than upon inductive positiveness for our working hypothesis. What some of us have observed, who see with psychological eyes, or, to retain my metaphor, who feel with psychological hands, I have tried to set forth briefly. I have even hazarded a theory of reconciliation of the known facts. I shall now listen with the utmost interest to what my colleagues have to say about the physical and chemical aspects of the same condition. Perhaps after many years of continued study and comparing of notes we shall have arrived at a comprehensive view of the condition in which arterial hypertension is one symptom.

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## THE TREATMENT OF ACUTE GLOMERULONEPHRITIS IN CHILDREN\*

JOHN D LYTTLE

Assistant Clinical Professor of Diseases of Children College of Physicians and Surgeons

Two hundred and nineteen cases of Bright's disease have been diagnosed during the past eight years at the Babies Hospital. This number does not include patients with purulent nephritis or chemical poisoning. These patients with Bright's disease were grouped according to the commonly accepted classification as follows:

Acute Glomerulonephritis	144
Acute → Chronic	2
Chronic Glomerulonephritis	29
Nephrosis	46

There is no good reason to attach much importance to these figures since the great majority of patients with acute nephritis are probably not seen by the doctor. In practice and in the clinic we see the child with a severe infection and a mild nephritis disclosed by routine examination or more rarely the child whose nephritis is severe enough to bring him to the clinic or physician. Our figures simply illustrate the general experience in the eastern cities and show that acute glomerulonephritis and nephrosis are childhood diseases, in adult practice these conditions are relatively uncommon. These figures also show how rarely it is possible to observe the transition from acute to chronic nephritis. I have no explanation for the figures of Snook and Addis who found that 40 per cent of their patients eventually developed chronic nephritis. I don't think that the difference in technique used in urinalysis accounts for the discrepancy. Perhaps the difference is regional. But chronic nephritis is a complicated controversial problem and my subject tonight is a discussion of some factors in the etiology and treatment of acute glomerulonephritis.

There is abundant evidence that acute glomerulonephritis is preceded and accompanied by hemolytic streptococcus infection with great regularity. The most common seat of infection is in the upper respiratory

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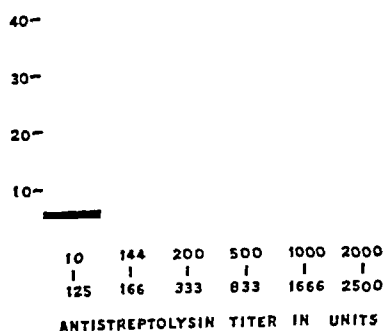
ANTISTREPTOLYSIN TITER IN 116 CASES  
OF ACUTE GLOMERULONEPHRITIS

CHART I

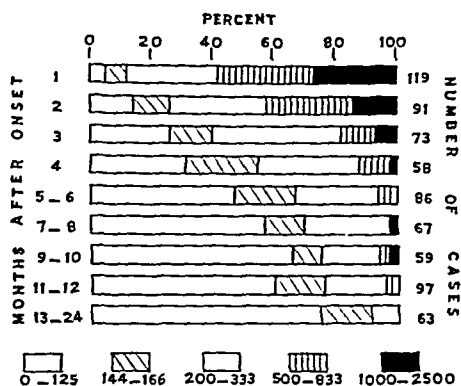
TITER OF ANTISTREPTOLYSIN FOLLOWING  
ACUTE GLOMERULONEPHRITIS

CHART II

fact and adjacent structures. Clinically, we know that the seasonal and geographical incidence of acute nephritis in children parallels that of streptococcus infection. There is no doubt that other organisms can stand in association with typical clinical and anatomical acute nephritis but the number must be small. With Doctor Seegal, Doctor E. N. Loeb and Miss Jost we have studied the antistreptolysin titer of the blood serum in acute nephritis. Chart I shows the maximum antistreptolysin titer of the serum in 116 consecutive cases of acute glomerulonephritis. Ninety-five of these patients are under thirteen years of age, twenty-one are adults. It has been found that in the great majority of normal individuals the antistreptolysin titer is less than 125 units. We think this chart which shows that 9 per cent of patients with acute nephritis have an abnormally high antistreptolysin titer indicates that in New York City the great majority of patients with acute nephritis have had a streptococcus infection preceding the nephritis. In chart II is shown the titer of antistreptolysin in the two years following the onset of acute nephritis. The percentage of normal antistreptolysin titers increases with time until in the second year they are 75 per cent. This period serves as a control for the group. So far as we can tell the variations in antistreptolysin titer are not related in any way to the severity or duration of the acute nephritis but are very closely related to the type and severity and persistence of the streptococcal infection. My object in showing these data is to illustrate the great regularity with which hemolytic streptococcal infection precedes acute nephritis.

The mechanism by which streptococcus infection produces nephritis is not known. It is not by direct bacterial invasion of the kidney. Escherich and Schick suggested as early as 1912 that it "might be a case of hypersensitivity of the organism which is expressed in the ability of small amounts of pathogenic substance to elicit clinical symptoms which at another time would be tolerated without any reaction." They pointed out the analogy between the sequence of events in postscarlatinal nephritis and that in the group of allergic reactions. This is the theory held by most observers today. Masugi and later Farr and Smadel working with nephrotoxic serum have produced a nephritis which clinically and anatomically closely resembles acute and chronic nephritis. However, until the disease is produced by hemolytic streptococcus in the experimental animal many questions must go unanswered.

With this brief discussion on etiology as an introduction I should like to go now to the question of the treatment of children with acute nephritis. Volhard states that in treating acute glomerulonephritis the problem consists in 1) Preventing the different dangers which may threaten the life of the patient during the acute stage, 2) preventing irreparable organic changes in the kidney. Volhard believes that early diagnosis and proper treatment during the acute stages is an important factor in the prevention of chronic nephritis and goes so far as to say that none of his patients seen and treated in the acute stage develop chronic nephritis. I am unable to convince myself from the evidence available that we can prevent the development of chronic nephritis. However, my experience has led me to believe that early diagnosis and adequate treatment at the proper time may prevent some of the fatalities in the acute stage of the disease.

Table I shows the mortality in acute nephritis in children as reported by different observers.

TABLE I

## MORTALITY IN ACUTE NEPHRITIS IN CHILDREN

<i>Cause of Death</i>	<i>Number</i>
Infection	28
Cerebral Edema	9
Renal Failure	12
Uremia (type not stated)	13
Cardiac Failure	6
<hr/>	
Total Deaths	68 (94%)
Total Number of Cases	722

It is seen that forty of sixty-eight deaths were due to cerebral edema, cardiac failure, uremia and renal failure and twenty-eight deaths were due to infection. It is a difficult matter to be certain of the cause of death in acute nephritis. In our own series where death was ascribed to cerebral edema, cardiac or renal failure, infection was an important contributing factor. Clinical experience leads one to believe that in any death from acute nephritis all four conditions may be present in some degree.

The conception that acute glomerulonephritis is but one manifestation of widespread capillary injury is rapidly gaining ground. We have not time to examine the history of this theory or the evidence for its support. The experimental results are conflicting, and much of the evidence is indirect. The physiological mechanisms are not known, but it seems probable that capillary constriction generally, as well as in the glomerular tuft, is an important feature. Baehr contends that unless extrarenal manifestations (edema, hypertension) are present the case is not true acute glomerulonephritis. And he would have us believe that all the glomeruli are involved in the process. From what we do know of etiology and pathogenesis and from anatomical studies in children it seems to me unreasonable to so limit the diagnosis of acute glomerulonephritis. It is known that this disease is an acute often explosive process and that the extrarenal manifestations may occur and not be observed because the patient does not come to the clinic until they have passed. It is also well known that glomeruli do not function continuously and it is reasonable to assume that some of them may escape injury by the hypothetical circulating toxins. This is proven by the work of Oberling who found from a study of biopsy material that the damage was focal and not diffuse. We are concerned here with the fact that clinical manifestations of this generalized capillary involvement are seen in over half of the cases if they are carefully looked for, and in approximately 10 per cent of the cases cerebral and cardiac symptoms and renal shut-down are severe enough to warrant serious therapeutic consideration.

The symptoms and signs which point to cerebral participation in the arteriolar spasm are easily recognized and are present in some degree in over half the children with acute glomerulonephritis. Oliguria, a rising blood pressure, symptoms of increased intracranial pressure, such as nausea and vomiting, headache, somnolence, visual disturbances, slow respiration, and slow pulse are prodromal signs of cerebral edema. There may be an increase in peripheral edema, papilledema and nitrogen reten-



tion may or may not be present, and lumbar puncture may show increased intracranial pressure. When the condition becomes severe, coma, delirium, amaurosis, and convulsions may be added. At autopsy the brain is firm and weighs 20 to 30 per cent more than is normal for the age. The dura is tense, the convolutions are flattened, and the ventricles are compressed. This condition was formerly thought to be uremia, but Volhard showed that it could occur in the presence of normal kidney function and that the term uremia is therefore incorrect.

In the majority of patients urine volume is normal throughout the acute stages. In some patients oliguria develops and may proceed to anuria. This renal shut-down is a serious manifestation. I prefer the term renal shut-down for this condition and use the term true uremia for the condition where the kidney changes are advanced and irreversible. In a few children the nephritis takes a rapidly progressive course and reaches the terminal stage (true uremia) in a short time. But in the majority of children who have impaired renal function associated with anuria during the acute stage complete recovery can and does occur. This condition is best explained on the basis of arteriolar spasm and decreased blood flow through the kidney. As Loeb points out, this idea is supported by the fact that often the anuria is terminated and diuresis appears too suddenly to be explained by the subsidence of inflammatory lesions. Some degree of edema usually goes with this condition, there is failure to concentrate and nitrogen retention and hypertension are present.

In over 60 per cent of the patients with acute glomerulonephritis there is clinical, x-ray, or electrocardiographic evidence of cardiac involvement. The incidence of electrocardiographic changes and x-ray evidence of cardiac enlargement is dependent on the frequency with which such studies are made. In a small number cardiac insufficiency may appear suddenly or develop slowly and result in death. Cardiac dilatation without histological changes is the common finding. Dyspnea or dizziness when the patient sits up, hypertension, a low pulse pressure, or the poor quality of the heart sounds and a systolic murmur may be the only clinical indications of cardiac involvement. The symptoms of cardiac failure are easily recognized.

The anatomical changes, the etiology and pathogenesis of these three conditions are not well understood. The one common factor in all of them is hypertension and the one reliable objective guide to the state of the circulation in acute nephritis is the blood pressure. I think it is impor-

int for the clinician to realize that when hypertension is present in a child with acute nephritis there are also present these three real threats to life, the danger to the brain, the heart and the kidney

The successful treatment of cerebral edema was developed in this country by Blackfan. The plan of treatment given here is that advocated by Blackfan and Butler and will serve as a basis for the treatment of cerebral edema, cardiac and renal failure. Any patient with a systolic blood pressure over 115 mm of Hg, or whose blood pressure is rising, or who has any signs or symptoms of cerebral edema is given 4 to 8 cc of 25 per cent solution of  $\text{MgSO}_4 \cdot 7 \text{H}_2\text{O}$  intramuscularly. The dose is repeated if the blood pressure has not fallen at the end of two hours or if the blood pressure at a later period begins to rise. With the intramuscular injection 1 to 2 ounces of 50 per cent  $\text{MgSO}_4$  solution is given by mouth every four hours, until the blood pressure has remained normal for twenty-four hours or until catharsis results. If convulsions are present 1 per cent  $\text{MgSO}_4 \cdot 7 \text{H}_2\text{O}$ , 100 to 150 cc may be given by vein. This form of therapy is ineffective and contraindicated in all forms of chronic nephritis with hypertension, and the diagnosis should be made before therapy is pushed. Overdosage is indicated by slow, irregular respiration, if this occurs 5 to 10 cc of 5 per cent  $\text{CaCl}_2$  should be given intravenously. The physiological action of  $\text{MgSO}_4$  is not known. Experimental work by Rubin and Rappoport has shown that the inclusion of  $\text{MgSO}_4$  in the diet of rats inhibits the vascular spasm produced by ergotamine tartrate in rats not so protected. Whatever the explanation empirically we know that  $\text{MgSO}_4$  lowers the blood pressure, relieves intracranial pressure and increases urine volume.

With this plan of medication fluid intake should be liberal, between 1000 and 1200 cc per twenty-four hours. The caloric needs may be disregarded until clinical improvement and a return of appetite, when a regular diet may be given. Other measures for the relief of cerebral symptoms, such as lumbar puncture, venesection, and the infusion of 50 per cent sucrose are seldom necessary. Lumbar puncture is not without danger since the sudden withdrawal of large amounts of cerebrospinal fluid in the presence of increased intracranial pressure may induce the medullary cone phase and death.

Oliguria and even complete anuria is at times a difficult problem for the clinician. I have had no experience with diathermy, radiation of the kidneys, renal denervation or decapsulation. The hunger-thirst regime

of Volhard seems to me too drastic for children. In addition to the ordinary measures taken the infusion of saline or hypertonic glucose and  $\text{MgSO}_4$  intramuscularly or by mouth has seemed to induce diuresis but many times all that is necessary is a little patience.

For those children who have only slight evidence of cardiac involvement nothing more than complete bed rest is indicated. But if cardiac failure develops then in addition to  $\text{MgSO}_4$  given as outlined above food and fluid should be restricted, venesection is practiced, 50 per cent glucose is given intravenously and digitalis and strophanthus may be used. Chloral hydrate and morphine are good sedatives. I feel that insuring absolute rest will accomplish more for the patient than subjecting him to many procedures of doubtful value.

The other important cause of death in acute nephritis is infection, either *per se* or as a contributory factor present in the circulatory conditions just discussed. Infection and acute nephritis are inseparable but the relationships and mechanisms are unknown. Much has been written on this subject but no one is in a position to speak with authority. For practical purposes the question divides itself into 1) the management of infections during the acute stage and 2) the problem of foci of infection.

In some cases the infection is subsiding by the time the nephritis has appeared, and only conservative therapeutic measures need be considered. But in the majority of patients there is evidence of a complication of the original infection or of a new infection. Peters states it this way: "Nephritis does not usually attack those patients who have an uncomplicated convalescence (from scarlet fever or angina) but those who have a septic complication such as cervical adenitis, otitis media, etc., from which *Streptococcus* can be recovered." So in some patients infection is a major problem. A mastoiditis, a peritonsillar or retropharyngeal abscess may demand immediate operation. Even if renal function is impaired and hypertension with its threat of cerebral edema and cardiac failure is present, I believe that major surgical indications in these patients should be met at the appropriate time. In these circumstances the nephritis should be regarded as an indication, not a contraindication for operation. Early in the disease we can count on enough renal and cardiac reserve to take the patient through a severe operation. These reserves may not be present if we wait too long. We have never seen harmful effects follow operations performed during the acute stages of the nephritis. Blood transfusion and specific serum therapy may be used whenever they are definitely indi-

ated There is good clinical evidence that in the majority of cases the proper treatment of severe infection in the acute stages of nephritis has favorable effect on the course of the disease We have all seen dramatic improvement in the nephritis follow in a few days after a mastoid operation or the relief of a peritonsillar abscess But it cannot be said that such measures will prevent the development of chronic nephritis It is true that some of the children who progress to chronic nephritis have persistent or recurrent infection in spite of proper care early in the disease But it is also true that many children who have persistent or recurrent infection never develop chronic nephritis I can only say that adequate surgical treatment of infection in patients with acute glomerulonephritis is fully justified on theoretical and clinical considerations In my experience this practice has given uniformly favorable results, neglect has been disastrous

We have used sulfanilamide in a few cases of nephritis with active streptococcus infection The only thing I can say about it is that if renal function is impaired the level of sulfanilamide in the blood must be carefully watched Nor can it be stated that the use of this drug early in the course of streptococci infections will prevent the development of acute nephritis

The problem of foci of infection in children with acute nephritis usually comes down to the questions 1) Should tonsillectomy be performed? and 2) If so, when is the best time to do it? All agree that the usual indications for tonsillectomy are more easily accepted in a child with nephritis My own belief is that acute glomerulonephritis is an indication for tonsillectomy In hospital practice it seems to me a much safer plan to operate on all children In private practice other circumstances may justify a more conservative policy But I have not yet learned how to tell what is at the bottom of a tonsil by looking at the outside Since history, examination, and laboratory tests may be so misleading it would seem much safer to have the tonsils out in any event

There is a general belief that tonsillectomy should not be done during the acute stages of glomerulonephritis Some authorities wait for complete recovery or until improvement has stopped It seems to me that in the ordinary case the time for tonsillectomy is when the hematuria and albuminuria have diminished, when hypertension has subsided, and most important, when the throat is not acutely inflamed No rule can be made, but in the majority of patients this point is reached in the first two to four months after the onset of acute nephritis In certain cases there are definite

indications for early tonsillectomy When during the first few weeks of the disease the nephritis does not improve on a suitable regime, and the otitis or mastoid do not heal as promptly as expected, and when there are repeated attacks of pharyngitis with adenitis with or without exacerbation of the nephritis, tonsillectomy should be considered and performed at the earliest opportunity despite the activity of the nephritis Parsons and Barling state that "On general principles a focus which is definitely septic (e g, tonsils) should be removed as soon as possible, but each case must be considered as an independent problem Operations should not be undertaken during an acute attack of glomerulonephritis without very serious thought, but the general reaction is often surprisingly slight, and the practice is to be commended if the focal inflammation is quite definite and improvement in the kidney trouble is not taking place There is of course the danger of a very considerable reaction"

The objections to this early attack on foci of infection are in general that it makes the patients worse and specifically that it causes a flare-up in the urine But if one studies these patients carefully it is seen that the postoperative flare-up is mild and transient and is not accompanied by hypertension or edema, whereas a recurrence of the infection is usually accompanied by a real exacerbation of the nephritis In my experience I have not seen the evil results predicted by those who have not followed this plan, and therefore this criticism of early tonsillectomy seems invalid

I admit that we are ignorant of the mechanisms involved, and that no one can say that early tonsillectomy lessens the incidence of infection or prevents chronic nephritis In considering this problem the following facts seem pertinent 1) No one can tell which acute cases will progress to chronic nephritis, 2) Acute nephritis is almost invariably preceded and accompanied by upper respiratory infection or one of its complications, 3) Recurrent infection in the convalescent period has an unfavorable effect on the nephritis, 4) The development of chronic nephritis is at times associated with persistent or recurrent infection, 5) When chronic nephritis has become established any attack on foci of infection is useless These facts lead naturally to the conclusion that anything we can do to fight a condition so closely related to acute and chronic nephritis should be done and done as early as possible Only long continued observation will bring satisfactory proof, meanwhile one's clinical experience is worth something In our hands this plan of management has not been harmful and so far the results justify its continuance

In closing I realize I have omitted to say anything about the general measures taken in the management of acute nephritis. This is not because I think them unimportant but because I think they are well covered in the texts on the subject. I have stressed the problems of infection and circulatory disturbances in acute nephritis in children because they are inadequately treated in most text books and are neglected by many clinicians. My only excuse for spending so much time on the subject is the belief that the physician will realize these serious possibilities inherent in a child with nephritis; a more alert attitude will result in a lowered mortality.

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## PROCEEDINGS OF ACADEMY MEETINGS

### STATED MEETINGS

MARCH 3—*The New York Academy of Medicine Executive Session*—a] Reading of the minutes b] Presentation of the Academy Medal to Dr Bela Schick on the occasion of the twenty-fifth anniversary of the publication of his work on immunity in diphtheria c] Papers of the evening—d] The recognition of deficiencies in the first four vitamins and measures for prevention, Edwards A Park, Pediatrician-in-Chief, The Johns Hopkins Hospital, Baltimore, e] The specific prevention of diphtheria—fur-

ther observations and inquiries, John G FitzGerald, Director, School of Hygiene and Connaught Laboratories, University of Toronto, f] Variations in incidence in infectious diseases, James Payton Leake, U S Public Health Service Bureau

MARCH 17—*The Harvey Society (in affiliation with The New York Academy of Medicine)* The sixth Harvey Lecture, The Isolation and Properties of Tobacco Mosaic and Other Virus Proteins, Wendell M Stanley, Associate Member, The Rockefeller Institute, Princeton

## SECTION MEETINGS

MARCH 1—*Section of Dermatology and Syphilology* Reading of the minutes  
 Presentation of cases—*a*) New York University, College of Medicine, *b*) Miscellaneous cases  
 Discussion of selected cases  
 Executive session

MARCH 1—*Joint Meeting of the Section of Neurology and Psychiatry and the New York Neurological Society* Reading of the minutes  
 Papers of the evening—*a*) Ephedrine in the treatment of convulsive seizures, Israel S. Wechsler, Discussion by Foster Kennedy, S. Bernard Wortis, George Haslop, Emanuel D. Friedman, Israel Strauss, *b*) Surgical therapy in certain convulsive disorders, Ira Cohen, Discussion, Charles A. Elsberg, Joseph H. Globus, John H. Scarff, Israel Strauss, *c*) Perverse tendencies and fantasies—their influence on personality, Sandor Lorand  
 Discussion by Abraham A. Brill, Israel Strauss, Clarence Oberndorf, Foster Kennedy  
 Executive session

MARCH 9—*Section of Historical and Cultural Medicine* Executive session—*a*) Reading of the minutes, *b*) Nomination of section officers and one member of advisory committee  
 Papers of the evening—*a*) Peter Dettweiler (1837-1937) initiator of the rest cure in tuberculosis, S. Adolphus Knopf, *b*) Niels Stensen—his tercentenary, Anne Tjomsland  
 General discussion

MARCH 10—*Section of Pediatrics* Case report, Feeding the cleft palate infant with the aid of a dental plate, J. H. Sillman, D.D.S. (by invitation)  
 Papers of the evening—*a*) A preliminary study of stimulation of growth in short normal children and dwarfs, Josephine H. Kenyon, Discussion by Irving H. Pardee, *b*) The anaphylactogenic properties of cereal foods and breadstuffs, Bret Ratner, Discussion by Oscar M. Schloss, *c*) Bulbar poliomyelitis following tonsillectomy and adenoidectomy, Alfred E. Fischer, Maxwell Stillerman

(by invitation), Discussion by Sidney D. Kramer (by invitation)  
*d*) The diagnosis of blood dyscrasias by sternal marrow puncture, Peter Vogel (by invitation), Frank A. Bassen (by invitation), Discussion by Nathan Rosenthal

MARCH 15—*Combined Meeting of the Section of Medicine and the Section of Surgery* Executive session—*a*) Reading of the minutes, *b*) Appointment of nominating committee, section of medicine  
*c*) Appointment of nominating committee, section of surgery  
 Papers of the evening—*a*) Physiology and pathology of extracellular fluid, James L. Gumble, Boston (by invitation), Discussion by A. A. Weech (by invitation), Dana W. Atchley, *b*) Simple and accurate blood studies in surgical emergencies (shock, hemorrhage, trauma, burns, perforations, intestinal obstruction) as a guide to appropriate and adequate therapy, John Scudder (by invitation)  
 Discussion by William F. MacFie, Samuel Standard  
 General discussion

MARCH 16—*Section of Genito-Urinary Surgery* Executive session—*a*) Reading of the minutes, *b*) Appointment of nominating committee  
 Presentation of cases—The present status of cystometry, with special reference to microcystometry, Irving Simons  
 Paper of the evening—Ureteral transplantation  
 A resume of the indications and contraindications and personal experiences with the operation, Elmer Hess, Erie, Pa. (by invitation)  
 General discussion, Simon A. Beisler, Abraham Hyman, Thomas J. Kirwin

MARCH 16—*Section of Otolaryngology* This meeting held conjointly with the Section of Otolaryngology of the College of Physicians of Philadelphia  
 Reading of the minutes  
 Papers of the evening—*a*) Parapharyngeal hemorrhages, diagnosis and treatment, Louis Hubert, Francis W. White, Discussion by Warren B. Davis (by invitation)  
*b*) Treatment of carcinoma of the larynx, Rudolph Kramer, Discussion by Gabriel

Tucker (by invitation), c] Modification of the semilunar ganglion approach used in surgery of petrous pyramid, Martin F Jones, Discussion by Oscar V Batson (by invitation) ¶ General discussion

18—*Section of Orthopedic Surgery* Executive session—1] Reading of the minutes b] Appointment of nominating committee ¶ Papers of the evening—1] Painful hips, M N Smith-Petersen, Boston (by invitation) (45 minutes) b] Bone block for painful hips, Joseph B I Episcopo (30 minutes) c] Discussion, Philip D Wilson, Nicholas S Ransohoff, Alan DeForest Smith ¶ General discussion

21—*Section of Ophthalmology* Display of mammalian fundus plates—Demonstration of materials, methods and technique of art in relation to eye by various ophthalmologists and artists ¶ Executive session (8:30)—1] Reading of the minutes b] Appointment of nominating committee ¶ 1] Art in ophthalmology, Percy Friedenbergl (by invitation), b] Mammalian fundi, LeGrand H Hardy ¶ Presentation of cases—1] Choroidal hemorrhage simulating a choroidal tumor, Martin Cohen, Lewis W Crigler, b] An unusual case of retinal detachment with cyst formation, Walter Griffes (by invitation) c] Plastic repair of old laceration of lower lid (moving picture demonstration), Wendell L Hughes ¶ Paper of the evening—A preliminary report of the value of functional visual tests for the localization of supratentorial tumors of the brain (illustrated by lantern slides), Charles A Elsberg, Hyman Spohnitz (by invitation) Discussion, John M Wheeler

MARCH 22—*Section of Obstetrics and Gynecology* From the Memorial Hospital Executive session—Appointment of nominating committee ¶ Papers of the evening—1] Experience with radium therapy alone in cancer of the corpus uteri, Robert L Brown (by invitation)

Discussion, Nelson B Sackett, b] Management of the advanced case of carcinoma of the cervix, E L Frazell (by invitation), Discussion, Ira I Kaplan, c] Chorio-carcinoma, a report of seven cases, John A Kelly (by invitation), Discussion, Thomas C Peightal, d] Choice of treatment in fibromyoma of the uterus, William P Healy Discussion, James A Corscaden

#### AFFILIATED SOCIETIES

MARCH 16—*New York Section of the Society for Experimental Biology and Medicine at The New York Academy of Medicine, 2 East 103 Street* Vitamin B<sub>1</sub> metabolism in man Urinary excretion of B<sub>1</sub>, Alfred S Schultz, Robert F Light, Charles N Frev (introduced by I Greenwald) ¶ The effect of choline on the production of experimental atherosclerosis in rabbits, Alfred Steiner (introduced by Kenneth B Turner) ¶ Investigations on the pathogenesis of tetanus, Bernard Zuger, Ulrich Friedemann (introduced by Benjamin Kramer) ¶ Hemolytic properties of indol, Eric Ponder ¶ The diagnosis of venous-arterial shunt by the ether circulation time method, William Benenson William M Hitzig (introduced by George Biehr) ¶ Effect of cyclopropyne on intestinal activity in vivo, C I Burstein (introduced by Colton)

MARCH 21—*The New York Roentgen Society in affiliation with The New York Academy of Medicine* Presentation of interesting cases ¶ Paper of the evening—Cancer of head and neck, Douglas Quick Discussion, Hayes Martin (by invitation), William Harris, Maurice Lenz ¶ Executive session

MARCH 29—*New York Pathological Society in affiliation with The New York Academy of Medicine* Joint meeting with the New York Gastroenterological Association Papers of the evening—1] Heredity in cancer, Madge T Mucklin b] Experimental evidence on the relation between heredity and external factors in cancer, Clara Lynch

## DEATHS OF FELLOWS

CHARD, MARIE LOUISE 121 East 60 Street, New York City, born in Brooklyn, New York, January 6, 1868, died in New York City, January 20, 1938, graduated in medicine from the Women's Medical College of the New York Infirmary for Women and Children in 1895, elected a Fellow of the Academy May 5, 1904

Dr Chard was consulting surgeon and gynecologist to the New York Infirmary for Women and Children and a member of the Board of Trustees of that institution

Dr Chard was a Fellow of the American College of Surgeons, the American Medical Association, and a member of the County and State Medical Societies

EDGERTON, FRANCIS CRUGER 570 Park Avenue, New York City, born in Middletown, Connecticut, July 11, 1874, died in New York City, February 19, 1938, graduated in medicine from the College of Physicians and Surgeons in 1898, elected a Fellow of the Academy November 5, 1903

Dr Edgerton was consulting surgeon to the St Mary's Hospital in Hoboken. He was a Fellow of the American Medical Association, the American College of Surgeons and a member of the International Society of Urology, the American Association of Genito-Urinary Surgeons, and the County and State Medical Societies

GELBER, CHARLES NEUMAN 30 East 40 Street, New York City, born in Austria, June 2, 1891, died in New York City, March 3, 1938, graduated in medicine from the Long Island College of Medicine in 1913

elected a Fellow of the Academy, November 3, 1921

Dr Gelber was a Fellow of the American Medical Association and a member of the County and State Medical Societies

MICHAELIS, ALFRED 171 West 71 Street, New York City, born in Berlin, Germany, February 11, 1874, died in New York City, January 29, 1938, received the degree of Bachelor of Arts from the College of the City of New York in 1894 and graduated in medicine from the College of Physicians and Surgeons in 1898, elected a Fellow of the Academy February 7, 1907

Dr Michaelis was Assistant Professor of Otolaryngology at the College of Physicians and Surgeons and Attending Neurologist to the Vanderbilt Clinic. He was a Fellow of the American Medical Association and a member of the County and State Medical Societies

SCHROEDER, LOUIS CLAUSEN 50 East 72 Street, New York City, born in Philadelphia, Pennsylvania, April 14, 1881, died in New York City, February 25, 1938, graduated in medicine from the College of Physicians and Surgeons in 1911, elected a Fellow of the Academy, February 7, 1918 and designated a Fellow in Pediatrics in 1933

Dr Schroeder was attending physician to the New York Hospital and consulting physician to the St Luke's, Newburgh and State Reconstruction Hospitals. He was Assistant Professor of Clinical Pediatrics at Cornell University Medical College

Dr Schroeder, who held a certificate from the American Board of Pediatrics, was a Fellow of the American Medical Association and a member of the American Pediatric Society, the American Academy of Pediatrics and the County and State Medical Societies. He was a member of the Editorial Board of Preventive Medicine

BULLETIN OF  
THE NEW YORK ACADEMY  
OF MEDICINE



MAY 1938

THE FUNCTIONAL SIGNIFICANCE OF  
THE LYMPHATIC SYSTEM

*Harvey Lecture, December 16, 1937*

CECIL K DRINKER

Department of Physiology Harvard School of Public Health Boston Mass

IT is the first duty of a Harvey Lecturer to give credit to those who have gone with him upon many voyages of disappointment and occasionally of discovery. It is often hard to find the way to port alone, and while I have been selected to review our experiments, it must be understood I am merely the mouthpiece of all those who for the past ten years have labored with me in pursuit of a few of the elusive problems of lymphatic function.

The lymphatic system reaches its most complex development in mammals, and of all mammals man can probably claim the most extensive and elaborate lymphatic apparatus. Many of us are inclined to think of lymphatics, lymph nodes, and lymphocytes as a defense mechanism, and there is of course no doubt but that all these elements participate widely in infections and in inflammatory processes. But defense is by no means the whole story, and so it is necessary first to review what has been learned of lymphatic function in normal healthy subjects and second, to relate this to the reactions observed during infection and inflammation.

It should be part of such a summary to discuss one of the most fundamental problems of the lymphatic apparatus, namely, the function of the lymphocyte. The production, activity, and disappearance of these blood elements have been measured, so far, quite unsatisfactorily. But to summarize the experimental, clinical, and conjectural evidence upon lymphocyte function, interesting though the effort might be, is beyond the scope of this lecture, which deals with the movements and the chemical composition of lymph under varying conditions. The lymph nodes as effectors in this system find their place in the discussion.

### LYMPHATIC FUNCTION UNDER NORMAL CONDITIONS

In 1926, in Professor Krogh's Laboratory, I was assigned certain problems in relation to the permeability of the blood capillaries in the web of the frog, a subject very intimately involved with the problems of the composition and formation of lymph. It was then thought, in accordance with Starling's theory of the balance between capillary blood pressure and colloid osmotic pressure, that practically none of the plasma proteins passed through the wall of the capillary. But this conception did not fit the performances of the lymphatic system in the frog. These animals have no lymph nodes. The lymphatics are a simple, subsidiary circulatory mechanism and are steadily engaged in moving fluid which leaves the blood capillaries back again to the blood. It has been estimated that fluid equal to fifty times the total blood plasma may leave the capillaries and pass through the lymphatic system in twenty-four hours.<sup>1,2</sup> This means a very steady delivery from the blood, and when lymph was collected and analyzed, as was readily done by tying cannulas in the crural lymph spaces at the ankles and then placing the frog head up at an angle of  $30^\circ$ , it was found that the lymph always contained albumin and globulin, that it clotted, and that the protein concentration while variable averaged about one-half that of the blood plasma.<sup>3</sup> In the frog one can stop the lymph hearts with curare. This prevents the return of lymph to the circulation. If the condition is sustained the animal dies through loss of blood volume. It simply converts all the plasma to lymph. Furthermore, if one curarizes a frog, ties cannulas in the crural lymph spaces and in the abdominal vein, it is possible by gentle infusion of Ringer's solution through the vein cannula to wash practically all of the protein out of the blood, which it does not reenter lacking normal lymphatic function. It can be concluded, then, that in the frog the lym-

phatic system is engaged steadily in returning blood proteins to the blood, and that in the absence of normal lymph function these substances will accumulate extravascularly. When one turns to the mammal, in such regions as the skin and subcutaneous tissues, lymph does not circulate with a rapidity remotely resembling what is found in the frog. At the same time, lymph collected from such regions always contains the blood proteins, and if lymph drainage is blocked protein will accumulate to values as high as 5 per cent. Here again an important feature of lymphatic function is the steady movement of extravascular protein back to the blood.

In 1930, we began to attempt to collect lymph from many different regions in the dog, being confronted with the fact that thoracic duct lymph, upon which most of the classical lymph physiology had been based, represented a rather special case, being in the mammal the most vivid surviving evidence of an active circulatory function on the part of the lymphatics. So far as can be told, the blood capillaries in the intestines and perhaps, too, in the liver are permeable to protein to a degree resembling those in the frog. With this goes the fact that the intestinal lymphatics must carry fat. In an anesthetized animal lacking massage, or passive movement, I believe that almost all of the thoracic duct lymph comes from the abdominal organs. Practically none will flow in from the extremities and but small amounts will be added from the neck, from the heart, and possibly from the lungs.

Obviously, to get at the fundamental qualities of lymph and the conditions for its production it was necessary to get away from the thoracic duct. There was nothing new about this idea. As is the case in so many modern techniques in physiology, our cannulations and methods of collection can, in their main features, be found in Ludwig's *Arbeiten* in the seventies of the last century. But it was much easier for us. We made fine quartz cannulae. We had good binocular magnification and we had good anesthesia both local and general. And finally, there were both physical and biochemical methods for defining the composition and properties of the small amounts of lymph which could be obtained through such cannulations.

The most dependable figures on the amounts of lymph collectable per minute—by which I mean lymph from neither the thoracic duct nor an abdominal vessel—necessitate collection under normal conditions of lymph flow, and this was accomplished by cannulating a lymphatic



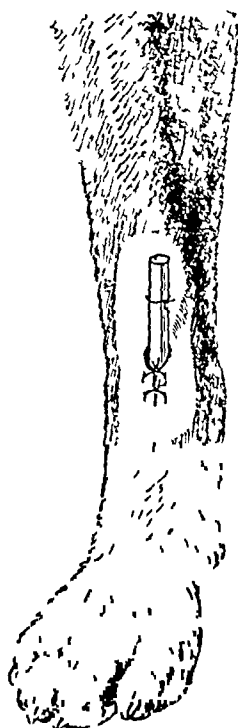


Fig 1 Cannula in a lymphatic draining part of the front foot of the dog (From Drinker, C K and Field, M E Lymphatics, Lymph and Tissue Fluid Baltimore, Williams & Wilkins, 1933, p 89 )

Fig 1

in the foreleg of a dog under local anesthesia, as is shown in Fig 1. With such a cannula in place a dog may walk or run during many hours of observation, thus contrasting periods of rest with periods of activity, periods of normal venous pressure with periods of high venous pressure and even perhaps periods in which what has been called "tissue pressure" is increased.

The results of such observations can be represented quite fairly in several figures taken from many experiments. In the first case, Fig 2, one sees what may be regarded as average normal lymph flow and the thing that is significant is that the amount of lymph which is really destined for the thoracic duct is exceedingly little. McMaster<sup>4</sup> and his associates have shown that appropriate substances injected intracutaneously may flow out through lymph pathways with astonishing rapidity. These quick spreads of foreign material from a central point have always been the result of an increase, even though slight, of tissue fluid pressure. They indicate most beautifully the extraordinary openness of the lymphatic system, and its availability as a path of movement for

Fig 2 Per cent of protein and milligrams of lymph produced per minute from dog prepared as in figure 1 Left leg cannulation and lymph collection May 3, 1937, right leg May 4 At the left-hand arrow the rate of walking was increased, as shown by the peaks in lymph production from the right leg and in alternate periods reduced to the earlier level Rapid walking ceased entirely at the right-hand arrow

Blood protein 5.68 per cent Lower ordinates, milligrams of lymph per minute, upper ordinates, per cent protein, abscissa, minutes

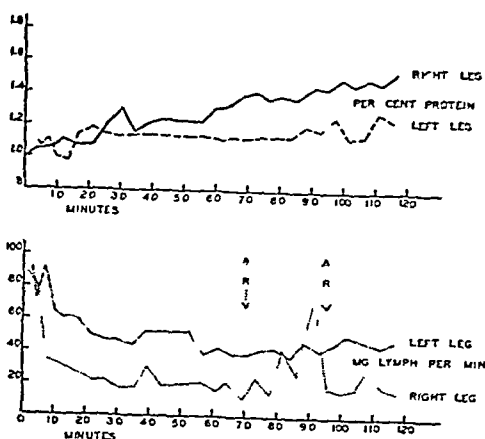


Fig 2

Fig 3 Per cent of protein and milligrams of lymph produced per minute from a dog prepared as in figure 1 Left leg cannulation and lymph collection April 20 1937, right leg April 23 At the left-hand arrow L venous pressure was increased to 80 mm Hg in the left leg, and this pressure was released at the right-hand arrow L In the right leg the two arrows R indicate the same manoeuvre Blood protein concentration 5.32 per cent Lower ordinates, milligrams of lymph per minute, upper ordinates, per cent of protein, abscissa, minutes

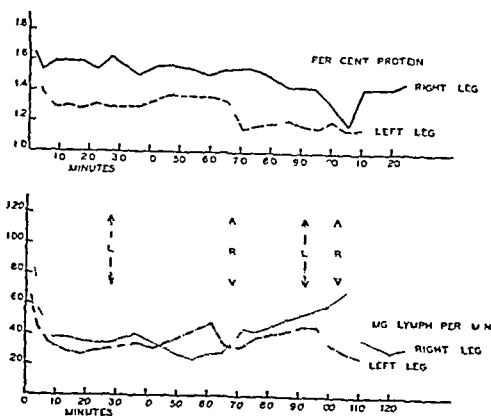


Fig 3

Fig 4 Per cent protein, milligrams of lymph, and milligrams of lymph protein collected per minute from a dog prepared as in figure 1 At the left-hand arrow venous pressure was increased to 80 mm Hg, and at the right-hand arrow released to zero Blood protein concentration 6.79 per cent Right ordinates, lower curves, milligrams of lymph per minute, upper curve, per cent protein Left ordinates, milligrams of lymph and protein per minute Abscissa, minutes

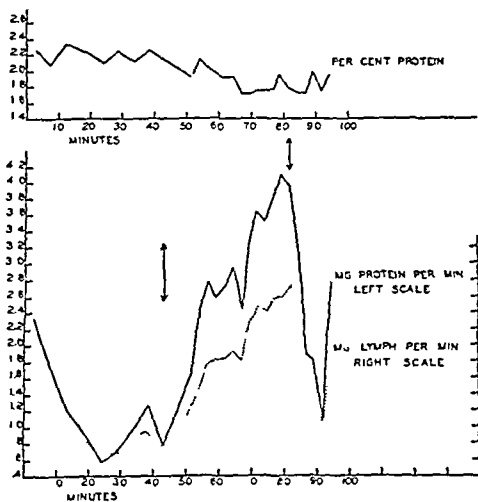


Fig 4

all sorts of abnormal tissue entrants. They do not give any actual indication of the movement of lymph out of a part which depends upon the entrance of lymph into valved vessels and then upon the effects of massage, motion, or swelling. Turning to Fig. 2 certain things are evident. First of all, after twenty minutes of walking at a uniform gait the amounts of lymph collected per minute become very uniform and the protein concentration, particularly in the left leg, does likewise. In the case of the right leg, observed a day later, at the arrow R, periods of rapid walking were alternated with the former uniformly slow rate. Increase in activity caused a corresponding increase in lymph production. In Fig. 3, an experiment is shown in which a left forefoot lymphatic was cannulated and at the left-hand arrow venous pressure was increased to 80 mm Hg. In this case, there was but a slight increase in lymph production as a result of this maneuver, and a delayed but equally slight fall in the concentration of lymph protein. At the right-hand arrow L the tourniquet causing venous pressure increase was released. Three days later the same experiment was performed on the right foreleg, venous pressure being increased to 80 mm Hg at the left-hand arrow R and released at the right-hand arrow R. The result was quite similar to that obtained on the left leg. It will seem strange that such a radical increase in venous pressure had so little effect but such is often the case. Apparently there are animals which resist alterations in lymph flow and composition with extraordinary success and such dogs behave very much the same upon successive days. Fig. 4 displays a very different sort of dog, one reacting according to conventional expectation. In this instance but a single leg is shown. At the left-hand arrow venous pressure was increased to 80 mm Hg, and at the right-hand arrow this pressure was released. Lymph flow increased from 38 to 230 mg per minute, and the total protein found in minute volumes of lymph increased from 0.77 mg to 4.2 mg per minute. These changes have an interesting relation to one another. Lymph flow increases in the ratio of 1 : 6.0 and lymph protein, collected per minute, in the ratio of 1 : 5.4. It is hard to escape the idea that during this period, when re-absorption of water by capillaries has not taken place, the filtrate from blood capillaries in the foot has had a protein concentration in the neighborhood of 1.8 per cent. Further, in view of the rapidity with which lymph production increased, it seems that just prior to the increase in venous pressure the capillary filtrate must have been high in protein but not so high as in the lymph.

owing to the fact that the latter concentration reflects absorption of water

The skin lymphatics exist as a meshwork over the whole body. So far as is known, this large lymphatic basin always contains lymph, and since the communication is so general, reactive substances in one part may eventually reach another. But it does not seem there can be any adjvants of this spread save movement, massage or swelling with accompanying increase in tissue pressure. The subcutaneous lymphatic network is thus an enormous potential route for distribution of extravascular material, but there is neither reason nor evidence for rapid directed movement of lymph through it under normal circumstances of rest.

The illustrations of lymph flow which appear in Figs. 2, 3 and 4 are a fair average of experience if lymph is collected from draining trunks in normal unanesthetized animals, but as has been indicated, surprising things are seen as such experiments are done over and over again. Dogs as classified from the point of view of lymph production by our laboratory assistant of many years, Louis Freni, are wet or dry. No one has seriously attempted to relate failure of lymph production to diet, fluid intake or any other existing or induced condition. Mr. Freni's classification is, however, a fact, and any one carrying on similar experiments will encounter animals in which lymph flow from draining channels will be negligible and others from which lymph flow will be surprisingly free. The giving of intravenous saline and copious water by mouth will not convert a dry dog to a wet one. These variations in lymph production in normal animals are vastly interesting, since they perhaps express changes in the conditions governing production and absorption of extravascular fluid which go beyond our present ideas upon these subjects. It is difficult to get away from the possibility that there are differences in the nervous regulations of the capillaries at different times and that these may cause delivery or absorption of tissue fluid. If, for example, arteriovenous anastomoses were freely open in a part, shunting blood away from capillaries, then capillary flow and pressure might be reduced and conditions made favorable for the absorption of water. If, on the other hand, such anastomoses were closed, then the full filtering capacity of the blood capillaries would become available provided an extreme degree of general constriction was not present. It is a question, too, whether the vasomotor control of arterioles, capil-

laries, and veins always operates in the same way or whether at times a single element in the triad gets the better of another. While such an expectation is perhaps reasonable, there is but little actual evidence for it. For example, it has been shown that acetylcholine has a possible constrictor effect on veins, and Haynes,<sup>5</sup> in 1932, found that acetylcholine injected into the artery to a part at once increased lymph flow. Fleisch<sup>6</sup> had indicated this might be due to a constrictor effect upon venous capillaries and small veins. If nerve impulses or chemical substances could induce mechanical relations which might cause changes in the nature of the fluid delivered from the blood capillaries or in the possibility of re-absorption of fluid by these elements, then there would be a basis for the idea that rapid changes in the composition of the tissue fluid were mediated by nerve impulses. In 1911, Stewart<sup>7</sup> showed that if one hand was exposed to cold or heat the blood vessels in the opposite hand dilated. This he attributed to a vasomotor reflex. No one has attempted to correlate such reflex vasomotor changes with changes in the fluid leaving a part through the lymphatics. Our own experiments, so far, have failed to illuminate the problem, though frequently we have believed we had evidence on the immediate change in the lymph caused through a variety of nervous reactions. Yet always on more complete analysis our experiments have broken down.

The chemical and physical properties of mammalian lymph have been measured since the seventies of the last century, but not with any great degree of accuracy until recently because of methodic difficulties. The relation between lymph and blood from certain regions outside the thoracic duct are shown in Tables 1 and 2. These tables, it seems to me, require emphasis in only one direction, namely, that lymph essentially reflects the composition of the blood plasma making allowances for dilution.

So much, then, for the formation and chemical composition of lymph in the normal animal. There is a further important point in relation to the question of lymph drainage. The lymph route is the one chosen for removal from the tissues of all sorts of foreign material which does not enter blood vessels. The familiar deposition of carbon particles in the lung lymphatics and tracheobronchial lymph nodes are to the point. I need not pursue the argument through experiments on the great serous cavities, the joints, etc., it is evident enough that the lymphatics begin to be a pathway as soon as abnormal and non-diffusible substances reach



TABLE 2

*Average Concentration and Osmotic Pressure of Proteins in Serum and Lymph* (Field, M E, Leigh, O C, Heim, J W and Drinker, C K  
The protein content and osmotic pressure of blood serum and lymph from various sources in the dog, *Am J Physiol*, 1934, 110 174)

	Albumin	Globulin	A/G ratio	Lymph/serum ratio	Total protein	Total osmotic pressure	Osmotic pressure per gram protein	Non protein nitrogen
	grams per cent	grams per cent			grams per cent	mm H <sub>2</sub> O	mm H <sub>2</sub> O	mgm per cent
Blood Serum								
Average 13 animals	3.61	2.63	1.46		6.25	306	49.1	38.9
Thoracic Duct Lymph								
Average 11 animals	2.45	1.54	1.72	0.65	4.00	191	48.4	39.0
Intestinal Lymph								
Average 2 animals	2.42	1.56	1.55	0.64	3.98	197	49.6	
Liver Lymph								
Average 4 animals	2.89	2.51	1.23	0.84	5.32	174	32.9	
Cervical Lymph:								
Average 13 animals	2.46	1.26	1.96	0.58	3.63	160	43.7	37.4
Leg Lymph								
Average 8 animals	1.20	0.71	1.81	0.296	1.91	100	51.5	

tissues

The general circumstances regarding the permeability of blood and lymph capillaries to visible particles seem to me to require, shall we say, in, or better, actual establishment. To illustrate. If calcite particles, pneumococci, and other non-motile materials are injected into the blood stream they can be recovered from lymphatics within an hour's time.<sup>8</sup> No evidence is available that phagocytosis has anything to do with this movement, which involves penetration of the wall of blood capillaries, possible brief sojourn in the tissue spaces, and then, if there be exercise or massage, penetration of the wall of a lymph capillary. There is no indication that such transfers involve the slightest leakage of blood proteins. The particle seems to pass through the endothelium much as a needle may be passed through a film of gelatin. There is no hole during the passage and none is visible when it is finished. The directed tendency of particles and colloidal solutions to move toward lymphatics is quite extraordinary. For example,<sup>9</sup> if the cervical lymphatics are cannulated in an anesthetized rabbit so that the lymph from these vessels may be collected, and then a suspension of Type III pneumococci is instilled into the nose, the organisms can be recovered from the cervical lymph within an hour but do not reach the blood until several hours have passed. To make the rapid journey to the lymph, a mucous membrane must be passed and a lymph capillary entered. The mechanism of such a transit is still wholly mysterious. Even more dramatic is the result when a normal cat is anesthetized with nembutal, the cervical lymphatic trunks cannulated with the cannulas pointing toward the head, the esophagus tied, and the trachea cannulated. If under such circumstances a centimeter of 3 per cent trypan blue in physiological saline is instilled gently into the nose, the cervical lymph displays strong blue coloration in fifteen to twenty minutes.

In summary, then, the lymphatic system in mammals in the light of modern experiment apparently operates as follows:

1. Such blood proteins as leave the capillaries to enter the tissue fluid are removed by the lymphatics. Under normal circumstances this function is called into play by changes in position, movement, either active or passive, and tissue pressure. In complete quiescence as in sleep or anesthesia lymph drainage is negligible, except from the abdominal region where intestinal movements are very potent in pumping the lymph into the thoracic duct.



2 The composition of lymph is that of dilute blood plasma. This is due to the filtration of products from the blood, and not, as has been suggested, to their universal production in the tissues. Too many experiments on alterations of lymph flow and composition depending upon changes in blood flow, pressure, and composition exist to require emphasis upon this point. There is no evidence in favor of it and no evidence in favor of selective phagocytic action on the part of lymphatic endothelium.

### LYMPHATIC FUNCTION UNDER ABNORMAL CONDITIONS

In 1932, I undertook, with my associates, to display some of the functions of the lymphatic system through a very old type of physiological attack, namely, the ablation of lymphatic function in a part, our conclusions as to the normal being dependent on what failed to happen when the lymphatics were rendered functionless. Efforts to stop drainage by direct surgical methods have never been successful, and I believe that lacking the more persistent effects of infection, clinical edemas are never due to lymph block alone. Let me remind you of the excellent experiments of Reichert,<sup>10</sup> in Halsted's laboratory. He divided all of the tissues in the thigh of the dog except artery, vein, and nerve to break continuity as completely as possible. The tissues were then sewn together and healing took place. The leg distal to the section began to swell on the second day, the swelling reached a maximum on the fourth or fifth day, but by the eighth or ninth day had subsided completely. It was possible by ink injections to show that lymphatics had regenerated across the wound by the fourth day. Lymph drainage cannot be extinguished by such measures, even if coupled with radical dissection of the lymph nodes in the groin and along the iliac vessels.

In thinking over the problem several factors were clear. First of all, surgery alone could not get the better of the powers of lymphatics to regenerate. Second, where lymphatic obstruction seemed to be present, as in the case of tropical elephantiasis and of the non-filarial elephantiasis seen in the north, the condition almost invariably developed over long periods of time and was the expression of repeated or persistent attacks of some agent or other upon lymphatics and lymph nodes. It was thus fair to believe that experimental ablation of lymph function must follow what clinical observation had indicated as necessary.

The experiments devised were simple enough.<sup>11</sup> Repeated, centrally

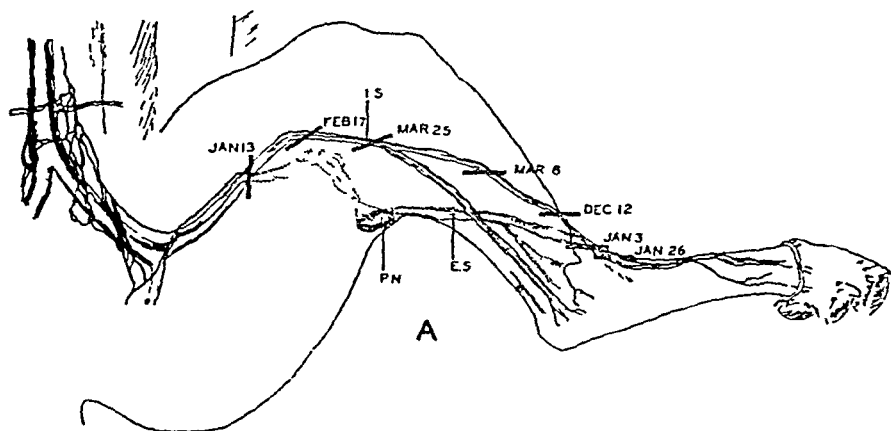


Fig 5—Lymphatics in the hind leg of the dog with sites of successive injections of quinine hydrochloride and crystalline silica. Each bar indicates a central injection of quinine hydrochloride and crystalline silica (From Drinker, C K, Field, M E and Homans, J The experimental production of edema and elephantiasis as a result of lymphatic obstruction, *Am J Physiol*, 1934, 108: 509)



Fig 6—Elephantiasis in a dog from repeated intralymphatic injections of quinine hydrochloride and crystalline silica (From Drinker, C K, Field, M E and Homans, J The experimental production of edema and elephantiasis as a result of lymphatic obstruction, *Am J Physiol* 1934, 108: 509)

directed injections of a suspension of finely divided crystalline silica in 25 per cent quinine hydrochloride were used (Fig 5) In this mixture the quinine caused a painless necrosis of the tissues and the silica induced progressive fibrosis just as it does when inhaled into the lungs By steady attack upon lymph nodes, normal vessels, anastomotic channels, and new vessels, lymphedema was produced and with it other things began to happen The first of these was fibrous overgrowth, typical elephantiac change, as shown in Fig 6, which eventually progressed to epithelial proliferation in the foot pads The second was the appearance of an astonishing susceptibility to streptococcic infection Perhaps it may seem that what these rather labored experiments accomplished was all known to clinicians before the experiments were done, but that is not the case Let us see what happens when lymphatic function is seriously interrupted As a result of repeated sclerosing injections edema appeared, and since there was no possibility of vein involvement this edema was a pure expression of what lymphatic obstruction could mean It developed slowly, and as the edema fluid which was easily obtained by subcutaneous puncture was examined we knew what the lymphatics would have been doing had the injections failed to obliterate them First of all, an ordinary pitting edema was established This was entirely unaccompanied by pain and was varyingly progressive In the beginning we were under the delusion that if our dexterity and endurance were great enough all the lymphatics in the legs of these dogs might be obliterated That I am sure was never accomplished What we really found was that if the central lines of lymph movement were systematically damaged, then peripheral lymphatics readily dilated, the valves became inadequate, and nothing could assure movement of lymph toward the blood except elevation of the part and the influence of gravity In addition to fluid accumulation, the leg at once began to grow and the growth was wholly at the site of fluid accumulation in the skin and subcutaneous tissues The tissue fluid gained steadily in protein until concentrations as high as 5 per cent were reached

Added to tissue growth, which was an inescapable feature of lymph block, another thing happened which has not been explained and apparently was wholly inevitable This was the matter of susceptibility to infection The dog has practically no bacterial enemies He is subject to virus, protozoal, and major parasitic diseases, but it requires preparation or mass infection to trouble him through the ordinary pathogeni

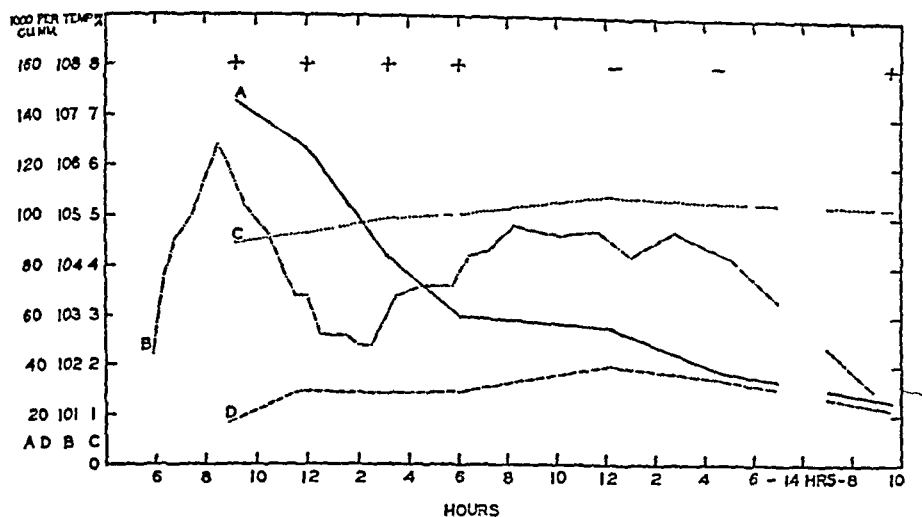


Fig 7—Details of a typical infectious attack in the lymphedematous and elephantiac leg of the dog shown in figure 6 Line A, leukocytes in the edema fluid in thousands per cubic millimeter, line B, rectal temperature in degrees Fahrenheit, line C, protein in the edema fluid in grams per cent, line D, leukocyte count in blood per cubic millimeter Ordinates as given for the different curves, abscissa, hours Plus signs indicate cultures of edema fluid positive for hemolytic streptococci minus signs, negative cultures (From Drinker, C K, Field, M E, Ward, H K and Lyons, C Increased susceptibility to local infection following blockage of lymph drainage *Am J Physiol* 1935, 112 74)

micro-organisms Yet when lymphatic obstruction had been established something quite different was in order Dogs, with this experimental interference with lymph flow, have attacks of streptococcic infection in the part involved For example, in Fig 7 there is shown the sudden, spontaneous infection of an animal with lymphatic obstruction Late in the afternoon it was observed that the dog was limping, favoring his elephantiac leg His temperature was at once taken and the course of events seen in Fig 7 followed This experience, repeated in other dogs and frequent in human patients, indicates all too clearly one of the unhappy consequences of lymphatic obstruction

In Fig 8 there is a similar chart of the reaction of the same dog to inoculation of the same streptococcus into his lymphedematous leg It had been shown previously that inoculation of large amounts of the same culture into normal parts had no effect, and this finding was con-

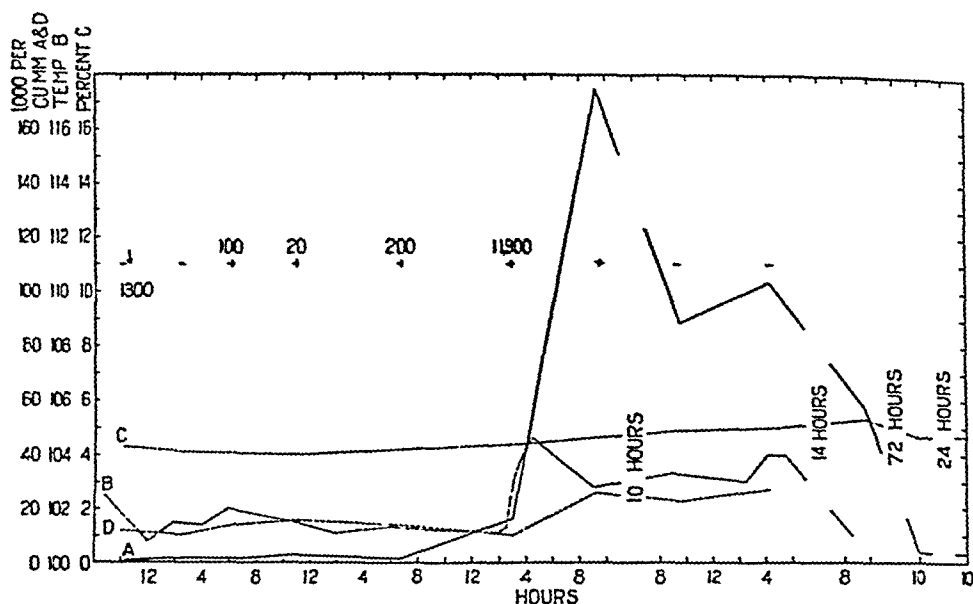


Fig 8—Details of an infectious attack in the dog subject to the spontaneous seizure shown in figure 7. In this case the attack was induced by injection of a dilute culture of the hemolytic streptococcus isolated during the previous spontaneous attack. Charting identical with figure 7. At the arrow 0.3 cc per kilogram of a dilute culture containing 1300 colonies of streptococci per cubic centimeter recovered from specimens of edema fluid (From Drinker, C K, Field, M E, Ward, H D, and Lyons, C. Increased susceptibility to local infection following blockage of lymph drainage, *Am J Physiol*, 1935, 112: 74.)

firmed upon other dogs. Notice the sudden rise in the temperature and in the leukocyte count in the edema fluid which followed steady increase of the organisms in the fluid. Cultures very promptly became negative following the febrile explosion, a possible reason why streptococci so seldom recovered from human cases experiencing similar attacks.

The results may be summarized as follows:

1. When lymphatics are obstructed the constituents of the lymph appear in the tissue fluid. What these all are no one knows, but increasing concentration of blood proteins gives a reliable indication of the progress of events. This has been shown in animals and in cases of elephantiasis.

2. With the appearance of lymphedema, deposition of fibrous tissue begins promptly and is progressive in direct proportion to the completeness of lymph block.

3 Regions of lymph block develop a surprising susceptibility to infection. So far as is known, this is streptococcic alone, but other organisms may be infective if they can enter the site of lymphedema.

All of these observations on the relation of the lymphatic apparatus to infection return us to the old question of why mammals have lymphatics at all. The predicament is plain enough. For example, in man the lymph from the outside of the foot enters draining lymphatic trunks which take it to a node in the popliteal space. This drainage way is open, highly organized, and quite uniform, yet I think that very few of us at any time in our lives will have an infection on the outside of the foot or lower leg with drainage into the popliteal node. It is hard to believe that such an elaboration of vessels as is existent in the area in question and in many analogous regions, exists solely for defense, this issue being one infrequently or never raised in the whole life of the individual. We are accustomed to adaptations which serve a certainty of use, but if defense is the use, then there is throughout the body infinite elaboration of a system which in the life of the individual may never have significant employment.

I believe that in mammals the lymphatic system retains its primitive position as part of the circulatory apparatus, but, because the permeability of peripheral blood capillaries to protein is not quantitatively great, this function is overlooked until lymph drainage becomes an important matter, as it does when infection is spreading or when the system is blocked and edema, elephantiasis, and hypersusceptibility to infection are inevitable.

Let me bring to your attention certain experiments performed during the last few years which, at least, do one thing. They illustrate the place of the lymphatics in certain unfortunate conditions, and the lack of knowledge in regard to the physiology and pathology of vascular and lymphatic permeability in certain situations. These experiments deal with both the lymphatics and the lymph nodes.

Rabbits were the subjects, anesthetized with nembutal. When a blood infection<sup>12</sup> is caused in a rabbit by a Type III pneumococcus, the blood and lymph pictures of the animal are as is shown in Fig. 9, and, while antipneumococcus serum is extremely effective in sterilizing the blood when injected intravenously, it is not efficient in sterilizing the lymph. It can be understood that while the blood capillaries in the major sense—excluding those of the intestines and liver—are permeable

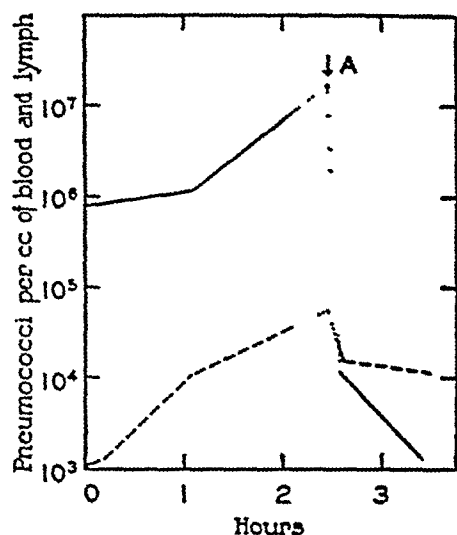


Fig 9

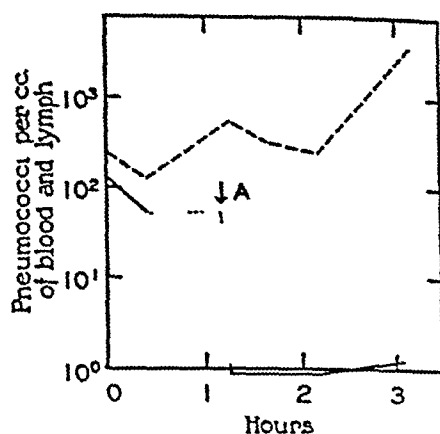


Fig 10

Fig 9—Solid line, number of Type III pneumococci in the blood, broken line, number of organisms in the thoracic duct lymph, dotted line, sections of blood and lymph curves, probable numbers of pneumococci before and after the time of antiserum injection. At A, 80 cc of Antipneumococcus Type III rabbit serum were given intravenously (From Drinker, C K, Enders, J F, Shaffer, M F and Leigh, O C The emigration of pneumococci type III from the blood into the thoracic duct lymph of rabbits, and the survival of these organisms in the lymph following intravenous injection of specific antiserum, *J Exper Med*, 1935, 62: 849)

Fig 10—An experiment similar to that in Fig 9. At A, 10 cc of Antipneumococcus Type III horse serum were given intravenously (From Drinker, C K, Enders, J F, Shaffer, M F and Leigh, O C The emigration of pneumococci type III from the blood into the thoracic duct lymph of rabbits, and the survival of these organisms in the lymph following intravenous injection of specific antiserum, *J Exper Med*, 1935, 62: 849)

to protein they are not permeable enough to permit the diffusion of more than a fraction of the antibodies necessary to check this bacterial infection. In a later series of experiments,<sup>15</sup> it was shown that when rabbits were infected with a virulent Type III pneumococcus given intravenously, the organisms were found promptly in cervical and in leg lymph. The isolation and survival of organisms in such regions seems to be due to the fact that the concentration of antibodies leaving the blood and eventually reaching the lymphatics is always well below that in the blood. Indeed, if current ideas as to the limits of normal

capillary permeability were followed it would be impossible to reach extracapillary regions with any but traces of the anti-substances injected intravenously or subcutaneously

While a fair delivery of such intravenous injections to the tissues may be expected, apparently killing concentrations will not be attained unless the anti-substances are of very high potency and reasonable diffusibility

### THE FUNCTIONS OF THE LYMPH NODES

The lymph nodes represent an addition to the lymphatic apparatus which is most puzzling. Let me remind you that as the scale of evolution is passed birds are reached before true peripheral organization of lymphatic tissue in glands is encountered, and then only in certain diving birds such as ducks and not in the ordinary domestic fowl with which we are familiar. Furthermore, even in the birds which do possess lymph nodes they are relatively isolated and insignificant affairs. Because of the fact that the lymphoid tissue in the mammal is so diffuse, it is discounted as an every-day influence in the body. Yet careful quantitations show that the total lymphoid organ in rabbits<sup>13</sup> makes about 3.3 per cent of the body weight. If this figure is transferred to a 150 pound man it means approximately five pounds of lymphoid tissue.

Why does man possess so large and so diffuse an organ? No one can say. At the present time, we are trying to find the normal lymphocyte production of isolated nodes, but this problem and the even more debatable one of the large delivery of lymphocytes through the thoracic duct to the blood and the simultaneous fact that the blood does not increase in lymphocyte content are mysteries at present beyond our knowledge.

That the lymph glands are effective filters is easy to show. It is a question whether or not any extravascular protein can get back to the blood vessels without going through a lymph node, and this possible restriction applies to all visible and invisible foreign aggregates in the tissues beyond the dimensions of inorganic or relatively simple solutes. In any event, it is sure that little or no material which reaches the tissues either through the blood capillaries or by accidental entrance from without gets back to the blood without first passing through a lymph node. This being the case, it is fair to attempt to appraise the nodes as filters, and we have made such experiments with a variety of particles



both animate and inanimate. In all cases it is sufficiently easy to show that the lymph nodes are quite effective.

Lymph flowing into a node from a number of afferent vessels reaches the marginal sinus and finds itself in a relatively large umbrella-shaped lake, where rate of flow at once becomes exceedingly low and every opportunity for settling occurs. In addition to this beautifully arranged mechanical effect there is the biological action of the endothelial phagocytes in the lymph node reticulum, so that even if relatively huge doses of streptococci are drifted in through afferent lymphatics the number escaping the node is practically negligible.<sup>14</sup> When actual lymph node infection is established, then the node may steadily feed organisms into the slow lymph stream. From being a filter the node becomes an unassailable cesspool draining eventually into the blood which in its turn may be reasonably capable of dealing with the organisms which enter it. Recent experiments<sup>15 16</sup> have shown that the lymph nodes have importance in the formation of antibodies, but it is all too evident that this function is often impotent and the nodes become centers of bacterial growth rather than the depositories of dead or agglutinated organisms.

In addition to filtration the nodes steadily pour lymphocytes into the lymph stream. Any degree of massage or of rapid lymph movement accelerates the delivery of the cells which border the sinuses and indeed of anything in the sinuses. How little massage is necessary is rarely realized. I am convinced, for example, that the movements of swallowing have much to do with the expression of lymphocytes and infectious material from the tonsils into the cervical lymphatic pathways.

So much, then, for the general features of lymphatic function which can be covered in the space of a single lecture. Perhaps what I have said makes it seem we really know a good deal about this system. It was in 1627 when Asellius in his vivisection of a "well nourished dog" first saw the widespread distribution of the lacteal vessels in the mesentery. Since his time William Hunter, Cruikshank, Ludwig, Heidenham, Starling and many lesser lights have broken lances with the problems of lymph production, lymph flow, and lymph node function. The great encouragement today lies in the increasing availability of direct methods of experiment, so that this circulation in mammals may be slowly taken to pieces physiologically, just as has been the case with the circulation of the blood.

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## RADIOTHERAPY OF TUMORS OF THE URINARY TRACT\*

BENJAMIN S BARRINGER

Urologist, Memorial Hospital

THE RADIATION therapy of urinary tumors—kidney, bladder and prostate—has taken on in the last ten years formidable proportions. Surgery has had more and more to acknowledge the potency of this valuable adjunct to its craft. This, the surgeon on the whole has been rather reluctant to admit. Changes from old established forms are difficult—even if the old methods are far from adequate.

There are perfectly good reasons for this slow acceptance of the tenets of a new art of healing. In it have been involved intricate problems of physics—almost unbelievable new precepts. For example the idea that a ray of energy could destroy a cancer in the interior of the body without affecting particularly the surrounding normal structures was new. So were the development of expensive new machines, and the utilization of radium, a newly discovered element. A quite extraordinary cooperation between the surgeon, the pathologist, the radiation expert, the physicist, the chemist, the biochemist and others was required. All this has involved a somewhat new and intricate setup in hospitals specially equipped to perform this function.

So the development of radiation therapy has been slow and hesitant, but the moving power behind it has been the relative impotency of surgery in dealing with urinary cancers. The present assured position of radiation therapy has been due to a certain partial success in dealing with certain phases of the cure of cancer. This success has been due in part to the method of approach established in cancer hospitals twenty years ago. These hospitals believe that radiation therapy must be in the hands of and actually performed by the trained special surgeon (radium therapy) or when used as an adjunct to surgery (Roentgen-ray therapy) it must be adequately understood by the surgeon and applied through cooperation of the surgeon and the roentgenologist.

\* Delivered November 11, 1937 in the Tenth Annual Graduate Fortnight.

A portion of the introductory remarks are taken from a chapter by the author in *Modern Urology* edited by Hugh Cribot.

We therefore see the reason for the specially equipped surgeon working in the specially equipped hospital, in other words, the cancer center

Radiation therapy as a whole is divided into two separate and distinct parts

First, radiation may be given from a source outside the body for the purpose of destroying tumors within the body. The two sources of this radiant energy are Roentgen ray and radium "packs." By this method no operation is done and no operative exposure of the tumor is made with the purpose of bringing the tumor nearer or more completely under the influence of the rays.

Second, radium or its collected and imprisoned emanation may be introduced directly into the tumor with or without the assistance of surgical exposure. Radium alone can be used in this way.

For all practical purposes external irradiation is limited to that produced by the so-called deep x-ray machines, either of the 200 K V type or the 700 K V type.

#### EXTERNAL IRRADIATION

If the tumor bearing organ were on the surface of the body, the problem of its irradiation would be simple. But we have to meet conditions as they are. The barrier which has to be considered is the skin. This is particularly vulnerable because of its relatively poor blood supply. The amount of irradiation that can be delivered to an internal cancer bearing area is limited by the amount the skin can stand. From this has arisen the term erythema dose, which means the amount of reaction, reddening or blistering that the skin undergoes following external irradiation. This skin tolerance is much greater than was originally thought. The skin will stand two or three times more than believed several years ago. Today in the first series of irradiation it is our habit to blister mildly the superficial skin areas. From this the skin easily and permanently recovers. Much more care has to be taken with subsequent irradiation and smaller doses have to be given.

Different organs of the body vary in the amount of irradiation they can receive on account of the different external ports through which the irradiation can be given. Thus the kidney can be irradiated through only three portals, anterior in front of the kidney, posterior behind the kidney and lateral. No irradiation can be given above or below the

have proved to be very radio-sensitive. The adult tumors are in a radio-resistant class and show only occasional and unpredictable regressions under external irradiation. Up to two or three years ago irradiation of Wilms' tumors gave extraordinary but unfortunately only temporary regressions in the size of the tumor. Because of the temporary nature of the regressions it was thought that if nephrectomy was performed at the height of the post-radiation regression two things would be accomplished. A heretofore deadly operation would become relatively benign, and more cures would result. The former estimate proved correct but the latter probably not. There are to date very few cures resulting.

The opinion was then expressed that these tumors were getting too large doses of x-ray in too short a time. This resulted in doses of 100 R or less being given to these tumors at a distance of 50 cm. through three portals of entry over a period of months. The children can stand this long irradiation very well. In a very few cases the tumors have shown semi-permanent regression. Possibly we are on the right track. One child has gone three years and one month (case of Dr. Walter McNeill) and one, a year under this regime. It certainly suggests that irradiation alone can cause the permanent regression we have all sought. Under irradiation alone the possibilities of metastases must be much reduced. With the operative removal of such tumors, tumor cells must often be set free in the blood stream.

### BLADDER TUMORS

These are semi-internal tumors which ought to be definitely diagnosed early in their destructive career. Hematuria is an early and prominent symptom. The tumors are not large as compared with kidney tumors. Can be seen through a cystoscope and can be diagnosed pathologically by pieces removed cystoscopically. As a class they are radio-insensitive. External irradiation has had little place in their control. Intrinsic or surface applications of radium applied through the cystoscope or the open bladder have been the means of control to date. Because most bladder tumors grow on the bladder base near the ureter openings or internal urethra, the treatment of these tumors by radium even if through the bladder opened suprapubically seemed to carry with it less danger than the removal of the tumors by operation. Radium treatment on the other hand has certain definite disadvantages, slough formation in certain cases, increase of infection, calcareous deposit on the radium

slough These to my mind seem to be over balanced by its advantages

The results of radium treatment in our hands, the radium either applied through the cystoscope where the mortality of the procedure is nil, or through the bladder opened suprapubically, are

3 year cures in 215 cases—69 or 32 per cent

5 year cures in 215 cases—52 or 24.1 per cent

The total number of cases in which the bladder has become cancer free are 96 or 44.6 per cent

These statistics include all cases large and small of bladder cancer (no papillomata are included) in which the tumor was believed confined to the bladder Many of the cases were in the class of so-called inoperability if we exclude total cystectomy

The pathological examination of the cured cases show

*Papilloma with atypical cells	5
Papillary Carcinoma	14
Infiltrating Carcinoma	16
Adeno-carcinoma	1
Grade I	10
Grade II	30
Grade III	12
Grade IV	2
No Pathology	6
	<hr/>
	96

The control of a greater percentage of cases would seem to be along the line of perfecting various methods of irradiation with probably some part to be played by external irradiation in the higher grades of malignancy

### PROSTATIC CANCER

Prostatic cancer shows a quite different picture

In 351 consecutive cases seen at the Memorial Hospital there were but sixteen cases (4.5 per cent) which might be called reasonably small, that were confined to the prostate and peri-prostatic region Twenty-six (7.4 per cent) were classified as medium size, that is well beyond the prostate proper, not too large and entirely within reach of the exam-

\* Only a part of these tumors have been graded

ing finger All of the remaining cases, 309 (88 per cent), were extensive, that is the tumor itself was very large or if the tumor was not large the extensions around the seminal vesicles or to the lateral pelvic walls were definite, or the bladder was secondarily involved, or the tumor arose post operatively, or bone or other metastases were present Combinations of these assured us of the hopelessness of the picture

From another angle, in one year seventeen out of twenty-nine cases were beyond any treatment whatsoever This is certainly a gloomy picture and to a certain extent reflects on the astuteness of the physician, who had the privilege of first examining the patient Both the medical student and the practicing physician must be better trained On the other hand one can hardly blame the physician too much because even after the diagnosis of prostatic carcinoma had been made and the patient is turned over to the specialist, he sees in most cases death inevitably supervene In many cases all that can be done is to ameliorate symptoms and make oncoming death more bearable Yet there are some rays of hope, twenty-nine (a little over 8 per cent) of these 322 cases were well from varying periods between three years and seventeen years and ten months That is, the prostatic condition was such as to make one believe that the carcinoma was controlled Nine went from three to five years, sixteen from five to ten years, and four more than ten years It is perfectly possible that not all of these cases are cured Time alone will determine

We know that while the majority of prostatic carcinomas are slow-growing and radio-insensitive, from 10 to 20 per cent are actively growing and radio-sensitive We know that in some cases the carcinoma remains confined to the prostatic and peri-prostatic region for apparently a long time (years?) with little tendency to metastasize

The aspiration biopsy if properly developed and interpreted is a great help in making an early diagnosis In 80 per cent of cases we can, by means of aspiration through the perineum, obtain prostatic tissue in sufficient quantity to make a diagnosis

Transurethral resection of the prostate has been a great advance in coping with urinary retention, while irradiation by radium of the prostate has developed and become sufficiently accurate to enable one to radiate a prostate without excessive pain to the patient External irradiation in sufficient quantity to be of any use has only developed in the last few years

It is not within the scope of this paper to discuss the operative removal of prostatic carcinoma. In a few selected cases the perineal operation of Young can be used to cure the disease. Successful removal of any large number of prostatic carcinomas by operation would seem to be out of the question. Extension of radiation therapy would seem to offer much more.

At present the irradiation consists of combining external irradiation with intra-prostatic irradiation by radium. This latter is by means of removable perineal needles or gold seeds introduced through the cystoscope through the open bladder or various combinations of these.

We might hope with these methods to achieve at least a 15 per cent five-year cure.



## PATHOLOGICAL PHYSIOLOGY OF BLADDER NECK OBSTRUCTION\*

W E LOWER

Cleveland Clinic Cleveland

THE ACT of micturition is an extremely complicated process which requires the harmonious coordination of both voluntary and involuntary muscles. Many factors may interfere with this coordination, resulting in either retention or incontinence of urine, and at no time may there be any pathological changes in the structures directly concerned in the act. The influence of environment upon the act of micturition is well known. It is a common occurrence to observe a patient who is absolutely unable to furnish a specimen of urine in your presence.

The effect upon urination of an inflammatory condition of the pelvis which does not directly involve the bladder neck is frequently observed, and retention of urine following operations for hemorrhoids, hernia, etc., is a common occurrence. Lesions of the spinal cord and even lesions of the central nervous system are a common cause of functional disturbance of urination. Thus, there is a great variety of conditions which may produce a pathological physiology of the bladder neck and interfere with the function of urination. In short, *controlled* bladder neck obstruction is a normal condition which is necessary for the comfort and health of the individual. It is only when this obstruction is entirely beyond the control of the patient that we speak of it as pathological. There are many local conditions at the bladder neck that may produce obstruction. The most common, of course, is the prostate gland and it is this phase which I desire to discuss, especially the *cause* of prostatic hypertrophy. As the prostate gland entirely surrounds the bladder neck, it is easy to see how certain changes in this organ could cause partial or even complete retention, either mechanically or by interfering with the mechanism of muscular control at the bladder neck, and I am not too sure but that the interference in the musculature of the bladder neck is more responsible than the actual mechanical block. If so-called benign prostatic hyper-

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trophy were part of the process of growing old, then all old men should have it but such is not the case. On the contrary, only about 40 per cent of men past fifty-five are so troubled, and even men much younger may have obstruction due to the prostate.

The theories formerly advanced as to the cause of the change in benign prostatic hypertrophy are not tenable and most writers have admitted that the real cause is unknown. It has long been known that if a young male animal be castrated, the prostate and seminal vesicles do not develop and if the testes of an adult be removed, the prostate and seminal vesicles atrophy. These results demonstrated the relationship between the testes and the secondary sex organs. In recent years, it has become increasingly evident that relationships between such organs as the testes and the prostate are further complicated by interrelationships with other organs, the pituitary gland in particular. It has been our aim to throw further light on the question of prostatic hypertrophy by studies of the intricate interrelationship which exists among the pituitary, gonads, and prostate. Some of our experimental investigations in this field are presented in this report. The chief of our Department of Biochemical Research, Dr. D. R. McCullagh, has done the chemical investigative work, and the technical work has been done by Dr. and Mrs. Eugene Cutuly. Mr. W. Kenneth Cuyler has assisted in making the assays.

The primary sex glands, the testes, consist essentially of two types of tissues: (1) the convoluted tubules, containing the reproductive elements and Sertoli cells and (2) intertubular elements, among which are found the interstitial cells. There is every reason to believe that in mammals the interstitial cells of the testes produce one or more substances generically referred to as androgens or male hormones. Recent advances in biochemical research have made possible the synthesis of numerous androgenic substances. These substances produce similar, but not necessarily identical, biological effects. Thus far, testosterone propionate is the most potent of all the synthetic male hormones yet prepared, and is one of the forms in which it is now used clinically. In order to avoid confusion, let us assume that the interstitial cells of the testis produce one male hormone and that this hormone is testosterone propionate. It is appreciated that this assumption may be proved to be incorrect, but even though it should be demonstrated that the interstitial cells elaborate a number of male hormones, the interpretation of our data will not be materially affected.

The function of the secretion of the interstitial cells, which we are

assuming is testosterone propionate, is to cause growth and development of the secondary sexual organs and characteristics. In mammals these include the prostate gland, seminal vesicles, scrotum, Cowper's glands, penis, vocal cords, distribution of hair, and others. There is no doubt that the accessory sexual organs are under the control of the secretion of the interstitial cells of the testis. Numerous investigations have established the fact that castration causes atrophy of the accessory glands and that male hormone supplied to castrated animals can prevent or repair such atrophic changes. In our studies, the accessory sexual organs which have claimed the greatest attention are the prostate, seminal vesicles and scrotum.

The secondary sexual organs are not the only structures which undergo gross and histological modifications following orchidectomy. In the rat the pituitary gland, too, shows definite changes after castration. Investigators do not concur on all points in this respect, but it is generally agreed that removal of the testes causes in the anterior lobe of the pituitary gland of the rat (1) the formation of vacuolated basophilic cells which are known as castration cells, and (2) transformation of chromophilic cells into chromophilic cells with basophilic granules. Divergent opinions are held as to the changes which occur in the eosinophilic cells. The formation of castration cells and the basophilism which occurs in the anterior pituitary after testicular ablation in the rat can be prevented or corrected by male hormone, such as testosterone propionate.

It may be said, therefore, that male hormone administered to castrated rats can, to a large extent, act as a substitute for the interstitial cells of the testis.

Castration is followed by certain changes because the interstitial cells are actually removed from the body. It is not necessary, however, to castrate a rat in order to induce atrophy of the prostate, seminal vesicles, scrotum, and other accessory sexual glands. Regression of these organs occurs just as rapidly following hypophysectomy as after castration. This effect is brought about because activity of the interstitial cells is dependent upon gonadotropic hormone. In the normal animal, gonadotropic hormone is supplied by the anterior lobe of the pituitary gland. When this organ is removed, therefore, the interstitial cells of the testes degenerate and cease producing male hormone. In hypophysectomized rats the interstitial cells of the testes which have undergone atrophy can be stimulated to activity by various means. Among the methods employed for this purpose may be mentioned the use of pituitary implantations,

crude pituitary extracts, purified hypophyseal gonadotropic hormone, pregnancy urine extracts, and pituitary hormone from parabiotic animals

One of our main objectives has been to discover how the size of the prostate can be increased or decreased experimentally. Since the prostate is controlled by hormone from the interstitial cells of the testes, and since the interstitial cells are controlled by the anterior lobe of the pituitary, we have been interested in devising methods by which the pituitary-gonadal relationship might be modified experimentally. A method which has proved to be very useful and which I shall discuss in some detail has been that of parabiosis.

Rats to be joined in parabiosis are anesthetized with ether and laid on a table facing one another. The skin on the uppermost side of each animal is clipped, and in each a long incision is made through this skin. The lateral abdominal muscles are thus exposed and a short incision is made through these muscles so that the body cavity is laid open. The cut edges of the muscles of the two animals are then approximated like two pairs of closed lips and fixed thus with interrupted sutures of silk. Wound clips are used to bring together the skins of the two animals. Starting three or four days after this operation, a few skin clips are removed every day until none remain. Healing usually requires one to two weeks in adult rats. Between the animals there is formed a bridge of muscular tissue in which capillaries from the two animals anastomose. It has been demonstrated that hypophyseal hormone can be made to pass from one animal to the other through such a capillary anastomotic network.

When two normal male rats are joined parabiotically no changes occur in either animal. If one of the animals be castrated, however, the secondary sexual organs of the normal twin become hypertrophied. This hypertrophy can be explained as follows. The pituitaries of castrated rats are known not only to undergo the gross and histological changes which have been mentioned, but also to become hyperactive as far as gonadotropic hormone is concerned. The pituitary of a castrated parabiont releases an excess of gonad-stimulating hormone which passes into the normal partner and there stimulates the testes to increase their output of male hormone. This increase in testis hormone is responsible for the hypertrophy of the accessory sexual organs. Evaluation of such results, however, is difficult, for one must take into consideration the fact that both parabionts possess pituitaries and that both pituitaries are producing gonadotropic hormone. This difficulty can be obviated if the test animal

is hypophysectomized

Results have been obtained on many pairs of rats of which one member has been a hypophysectomized twin. Our usual procedure is to begin an experiment with two normal littermates. After healing has occurred, one of the twins is hypophysectomized. In our experience the testes of a hypophysectomized parabiont joined with a normal partner almost always regress as rapidly as they do in non-parabiotic hypophysectomized rats. While atrophy of the testes may be slightly retarded, it is never prevented.

In order to prevent or correct testicular atrophy in a hypophysectomized parabiont, it is essential that such a twin be joined with a castrated male or female partner. When the donor twin is a castrate (regardless of sex), the following effects occur in a hypophysectomized test animal. (1) If the test animal is a male, both the tubules and interstitial cells of the testes are maintained in, or restored to, a completely normal condition. Such animals are capable of mating with female rats and siring normal litters. This fact is conclusive evidence that the entire genital tract of these animals is functioning in a normal manner. (2) If the hypophysectomized test animal is a female rat joined with a castrated partner, she will go into a state of continuous vaginal estrus or "heat," as shown by daily smears of cornified cells. It has been shown by other investigators that such females do not ovulate. They may, however, have sterile matings.

These reactions in hypophysectomized male or female parabionts have proved to be of great diagnostic value. In the hypophysectomized male test animal, for example, the scrotum, being under the control of the interstitial cells of the testes, indicates the degree of interstitial cell activity by the extent of its turgescence and flushing. The condition of the scrotum, in turn, parallels that of the prostate and seminal vesicles. Since the interstitial cells form only a small fraction of the testis volume, marked increases in testicular size largely reflect growth and development of the tubular components. Thus it is possible to judge changes which may occur in the genital tract from time to time without the necessity of sacrificing the test animal. While the situation in the female is not so clear, it is known that changes can be induced, so that the vagina can be caused to pass from an active estrous phase into a resting diestrous state.

Summarizing thus far, it may be said that an excess of hypophyseal gonadotropic hormone can pass from a castrated male or female rat into

a hypophysectomized test animal. The hypophysectomized male parabiont responds to this gonadotropic hormone by marked testicular activity which is outwardly manifested by increase in testis size and by growth and vascularization of the scrotum. When the partner of a castrate is a hypophysectomized female, this latter test animal responds to the high level of gonadotropic hormone from the castrate by exhibiting continuous vaginal estrus.

With various sex hormones now available in pure crystalline form, it was decided to use the parabiotic technique for testing their ability to inhibit hypophyseal gonadotropic activity. The important point to be determined was whether the hyperactivity of the pituitary in a castrated parabiont could be so inhibited as to result in atrophy of the genitalia in a hypophysectomized test rat. For this reason, various doses of male hormone (testosterone propionate) and female hormone (estrone) were injected daily or at intervals of several days into castrated parabionts. When adequate doses of either male or female hormones were so administered, it was found that very definite atrophic changes were induced in the hypophysectomized test animals. In hypophysectomized males, the testes shrank in size and ascended into the abdomen and the scrotum blanched and regressed. Within a period of a few days a hypophysectomized female joined with an inhibited castrate failed to show cornified vaginal smears and fell into a state of diestrus, characterized by a predominance of leukocytes in the smear. There was no doubt that male and female hormone were able so completely to suppress the gonadotropic hormone of castrated parabiotic rats that the genital organs of their hypophysectomized partners underwent the profound atrophy which is characteristic of unjoined and untreated hypophysectomized rats. These experiments serve to emphasize the reciprocal pituitary-gonadal relationship which must exist in the normal animal for the regulation of size and function of the accessory sexual organs in male and female animals.

The correlations of the various hormones in the body is still far from being clarified. The close relationship of the thyroid and the suprarenal gland is well known and the exact way in which the glands of internal secretion are associated with the pituitary is yet to be solved. That progress is being made is evident to anyone who keeps abreast of the massive literature on this subject. Just how long it will take to solve this problem will depend upon the accurate work of the various research groups now applying themselves along this line.

## THE MEANING OF MEDICAL RESEARCH\*

ALFRED E COHN

Member of the Rockefeller Institute for Medical Research New York

YOU may expect from me a description of discoveries, dramatic and exciting perhaps, of new diseases or of the mechanisms underlying diseases already identified, of new drugs which cure, like sulphanilamide, or of new operations which relieve or prevent devastating conditions. I could enliven this report by such narratives, as for example the great new insights which have resulted from studying the pituitary gland seriously. The investigation of this organ by Cushing who gave the forward movement a great impetus and by many other very capable and ingenious investigators, has resulted in the description of new ailments, has given point to the attempt to understand the interrelations of fluids and tissues and organs, in ways and to extents not dreamed of ten years ago, has made available agents of real power in adjusting defaulting or erring mechanisms. Or in a sense less pathological and more physiological, describe how great has been the increase in knowledge of the behavior of such important tissues as muscle and nerve. To speak of any one adequately would cost all my time. There are other ample provisions, however, for spreading that sort of information. My task is both simpler and more complicated. I am to speak of what research in medicine "means", what its nature is and what its purposes. And I take that to include an inquiry into its position in the complicated matrix of our social structure.

The ultimate meaning or purpose of medical research is to rid men of diseases, to protect them from maladies with which they are threatened, to relieve them of discomforts once they are established. There are many diseases, differing in the degree of dangerousness, differing in nature, differing in geographic distribution. There are pathological states to the existence of which we are sensitive—others which, for various reasons, we ignore. Then there is the character of education, having its sources and momentum in the contemporary scene, which makes men fit to undertake chiefly what is comprehensible in that scene. Researches are delayed

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because points of importance are missed, scholars being unprepared to comprehend them and to seize their opportunities. Researches are sometimes hurried, wasteful, and erroneous, because the idea is entertained that current equipment is adequate to deal with particular problems. The question of public versus private scholarship is important—less important now when the whole situation of research is better understood, and when private scholarship is recognized as being less private than formerly. Private refers both to financial resources sufficient to free scholars from the restrictions imposed upon the use of public funds, and to intellectual latitude which makes room for personal vagary, for unorthodoxy, which may not be tolerated even in an academic environment. But greater in importance than either, because essential, is the pervasiveness of current belief and opinion, current social need, the implications in the current social scene, which tend to influence or perhaps better which do not permit us to escape current intellectual compulsions. These are aspects of the intellectual life of which Hessen and his followers have made us aware.<sup>1</sup>

The meaning of medical research must regard these various social and personal aspects. It must regard also the nexus which exists between medical and other sciences. It must make an effort to understand likenesses and differences which characterize medicine in relation to those other sciences. It must analyze the situations, diseases and social pressures, to which energy is devoted and must describe the means, in men and facilities, which are available for carrying them out.

I propose to speak first of *what* we study, second of *how* we study it, third, of *who* does the studying, and finally in the course of this discussion for *what reason* does the study take place.

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When these far reaching issues and conceptions are being canvassed there must first be described certain situations which the world of

<sup>1</sup> It would be interesting and important to study the nature of social pressure, using this term in its widest sense, in the province of diseases. It is a point of view not strange to historians and students of social phenomena, but one not yet much employed in medical thinking. The illustrations in this essay have been drawn chiefly from communicable diseases and from a few other maladies differently grouped. But the relations exhibited by the development of knowledge of nutrition, or of understanding chemical processes on which nutrition depends, of agricultural growth, of social change in which the demands on the food supply of the less favored receive more sympathetic recognition—all these are matters which lie for analysis at the door of the critic. Here, as elsewhere, these and other factors require study in a complete account of the processes at work in a community.



diseases presents to investigators. It has already been suggested that these vary with time and place. We do not study those diseases which do not exist—or which exist elsewhere, or which exist no longer. The impulse to study a given disease or a given hygienic circumstance results from the danger or the damage which its presence causes. Epidemics of diseases like the black death or of poliomyelitis, or of influenza, or of cholera can scarcely or safely be ignored. But not many of the resources of this community are devoted to yellow fever or kala-azar, or African sleeping sickness. If these diseases were, by their maritime introduction, to threaten the local population, a study of them would be inescapable. They are studied though for several reasons, a general philanthropic motive, because, as in the opinion of Doctor Albert Schweitzer, restitution should be made by a people for the injury done another, because, to study them is imperative to preserve health along international trade routes. Pressure of some sort is usually experienced or is exercised when a study is undertaken.

Of the diseases which we do study, there are several kinds. It is of very great importance to understand that diseases cannot, all of them, be regarded as forming a system. They can be grouped, as indeed they are, to form several systems. The various systems have, superficially at least, little in common except that they transform the individuals whom they afflict.<sup>2</sup> Each group, on the other hand, exhibits traits which leave none or little doubt as to the relatedness of the members.

The center of gravity of interest in diseases has long, roughly for two generations, lain in *infectious* and *epidemic diseases*. To understand them and to cure them, the sciences which needed to be and which were and are actively cultivated are bacteriology and parasitology—these two in some respects similar. More recently diseases resulting from viruses, agents of far smaller dimensions than bacteria, have been added to the list. These diseases all depend on the invasion of animal and plant organisms by these agents. Parallel with bacteriology and parasitology, sciences roughly grouped as immunological have been developed, in which there have been studied the reactions, that is to say, the behavior of the hosts, plants and animals, which the infectious agents invade. Studies of immunity have gone farther though than the study of individual hosts when

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under attack. A science of epidemiology has grown alongside the other sciences in order to study the conditions in which societies of men, animals and plants chance to become prepared for invasion by infecting agents. These include external factors—climate, race, season, sunlight, and internal factors, the blood, the plasma, certain organs and tissues, heredity. To cope with these invasions, efforts in various directions have sedulously been made—with sera, which utilize the forces animal bodies themselves prepare for their protection, with chemicals, like salvarsan, like optochin, like arsphenamine, sulphanilamide—all synthesized with the utmost chemical skill, with natural pharmacal agents, chaulmoogra oil, quinine, salicylates. These are, in a sense, beginnings, the success of which points to the fact that the way of thinking about such problems as they represent, is sound and therefore encouraging. Much more may be expected from such efforts. Indeed, not more than auspicious beginnings have been made.

A point of importance, later to be referred to, is that the successes, still in many instances not more than partial, have been attained by delving below the surface of naturally existing phenomena, of appearances, to learn on what these diseases depend. The rewarding results have been that bacteria have been found, and protozoa and viruses. With this kind of knowledge as a background, substances of many sorts were and are being sought, to oppose the action of the invaders. Here are the rudiments, I may mention in passing, of analytical procedures. They represent something new in the study of diseases. Compared to the amount of energy which has been expended, the success so far achieved has, quite obviously, been extraordinary.

Infectious or contagious or epidemic diseases have often been characterized as acute. Acute means two things—that individuals are seized suddenly with disability, a matter of hours or minutes, and also that their duration is usually brief—though there are numerous exceptions, as tuberculosis, syphilis, and leprosy.

But there are long drawn out ailments, often called *chronic*, which fall into two great groups. Certain ones occur at all ages, like pernicious anemia or diabetes mellitus. But there are others which befall older persons exclusively. I designate these, “ailments” and not diseases, nor yet degenerative—two words often applied to them which I prefer not to use, for reasons which I hope later to develop.

To distinguish diseases merely according to their duration is a crude

conception But to do so has a use, for the time being Chronic has usually been intended to signify long drawn out Roughly, chronic and long drawn out mean the same thing From the point of view of patients and their families, duration is important, and from that of administrators concerned with the public health the distinction is essential Actually what is involved is the rate at which the processes in different maladies advance Chronic diseases or long drawn out maladies include a wide range of complaints Their duration is to be estimated, naturally, from their beginning to their termination, uninfluenced, when such examples are available, by treatment The group is diverse—there are, for example, the diseases of the blood forming organs—pernicious anemia, leukemia, thrombocytopenia, there is cancer, there is tuberculosis, there are the deformities of the joints, there are cardiac and arterial derangements, there are the defects which result from insufficiency or malfunction of the glands of internal secretion—the hormones in short, there are diseases of the nervous system It has been customary to divide diseases into three, or perhaps better two, main groups as I am doing, bacteriological and physiological both, but the latter especially employing physical and chemical techniques Chronic diseases fall into each of them These categories require in certain instances to be stretched fairly wide, in order to include all the varieties But they will serve for this discussion, especially if in studying bacterial diseases, the behavior of the host, immunology, is included, and if in the physiological ones, anatomical defects and malformations

It is sufficient, I think, to suggest that medicine deals with many kinds of conditions and that they fall roughly into the categories that have been indicated Of chief moment is that the classification, though rough, suffices to indicate that well characterized groups can be recognized and that, through this possibility, study is facilitated, perhaps made possible

Now it is generally understood and indeed it must be obvious that when a malady or any other natural phenomenon begins to be *analyzed* (analysis being the method essential to experimental research) very soon a level of organization is reached, less complex than the native state of a whole plant or animal, the study of which requires recourse to a chemical laboratory This is due to the fact that biological mechanisms, when the attempt is made to view them more simply, break down promptly to chemical processes In physiological diseases, especially those of the heart

and arteries, in parallel fashion, a stage is reached when mechanical and physical appliances are needed to help in understanding what is going on. To turn to chemistry, to mechanics, to physics, is to turn not so much to fundamental things as to machinery which underlies and which determines more complex, directly observable behaviors. These disciplines—physics, chemistry, immunology—constitute the techniques which are used to analyze, to reduce to simpler, more easily understandable mechanisms, the surface appearance of maladies. The fact that this is the situation in research in diseases constitutes a dilemma. To this problem it will be necessary to return.

I have referred to *two kinds of chronic diseases*—one which can occur at any age and one which is characteristic of the aged. Those diseases characteristic of the *aged* require especial description because, though they are not new, they are beginning to take on new significance. We grow older, all of us. As is well known, in the course of doing so we fall subject predominantly to several distinct kinds of disabilities. I pass over cancer, its nature and its ravages are in every one's mind. But what happens to the heart, the arteries and the kidneys, has been less clearly appreciated. I do not wish to discuss all the possibilities, all the theories. One theory ought I think to be more fully described. In the sense that everybody ages, aging has come to be looked upon as a natural phenomenon—natural as differing from accident or from chance. Since every one ages, aging is anticipated and the separate phenomena of aging are looked upon as predictable. This has been a subject of very active research in recent years. And the objectives in such researches have been twofold, first, to ascertain as precisely as possible a picture of what actually takes place and second, to discover what mechanisms are at work to bring about such results. I single out the arteries for more detailed description. That the arteries change is now universally known, especially the great artery of the body, the aorta. What is less well known is that the smaller ones do also. Arteries which have come in for marked attention in recent years are those of the heart—the coronary arteries. The walls of arteries may be thought of as having layers or coats. In the coronary arteries, for example, the first detectable changes take place in the innermost layer, its elastic membrane splits in two and does so rather early in life—in the twenties. From then on, more and more changes take place. At fifty or sixty these changes are advanced and have been termed arteriosclerosis. To one familiar with the succession of these appearances, it is possible to

tell their age, within a few years. Being able to do this is good evidence that there is nothing haphazard about the process. How are these systematic changes brought about? And how, assuming that they develop systematically, can they be prevented or delayed? To answer these questions, guesses have been ventured since very early times and to explain them, serious, far-reaching researches have been undertaken. But so far there are no answers, satisfactory to many scientists. Meanwhile the quest goes on, with intensifying earnestness. The problem, as I shall show presently, is urgent. What is true of the arteries of the heart is true of those of the brain. About other organs less is known. Progressive alterations, appropriate to each organ and tissue, go on throughout the body—beside the heart muscle, in the kidneys, in the liver—everywhere in short.

But changes in structure do not alone exhibit progressive alteration. Comparable ones can be observed also in the functioning of the body. The slow and gradual rise with age which the blood pressures exhibit are well known. Another striking one has recently been found in the nutrition of the body. Here, it appears that ptyalin, the starch-splitting ferment of the saliva, decreases between twenty-five and eighty-one (these are averages) to one thirty-fourth, necessitating, it seems probable, a very striking readjustment in digestion and food requirements in the aged. More intimate still are changes in behavior of the muscle fibers of the heart. It has been shown in dogs, for example, that as the animals grow older, the ability of this tissue to utilize oxygen diminishes significantly. Finally, as in changes in structure and in function, so also, it appears can changes in psychological performance be detected. Interest in this phase of growth has begun more recently, so that it would be rash to accept the results of preliminary studies. There can be little doubt though that this is a fruitful field for further investigation.<sup>3</sup>

Many regard it as an idle question, but it is one which should be put nevertheless—are processes so universal as are those identified with aging to be classed with diseases? Diseases are not constant, they wax and wane, new ones occur, old ones vanish, they are unlooked for, they are recovered from. Of the changes which accompany aging, none of these

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<sup>3</sup> This reference to psychological matters is brief because I am depending on other phases of this problem for illustration. But the place in human nature and in diseases which psychological deviations occupy can scarcely be over-emphasized. I am at one with those who wish to understand organisms as wholes and to return from the wilderness into which the requirements of thought in the Seventeenth Century naturally led us.

characteristics can be predicated. It seems better to weigh the question of the nature of this process of aging a while longer, before coming to a decision on its nature. Two ways of thinking are possible—that aging is an accident which can be prevented, or that it is not an accident and that, as the body increases in bulk and by so doing is said to grow, parallel changes are taking place within the body, in its most intimate recesses, which accompany that growth, and which themselves may be regarded as taking part in and perhaps constituting the phenomena of growth. In this sense the body grows continuously, changes, called differentiation, taking place in all its parts, the form of change passing from stage to stage without break until the final dissolution. This view urges that there is only one forward moving change—not, first growth and then degeneration, but continuous progressive differentiation. And growth so understood is not an accident, it is not degeneration—and it is not disease.

These old ailments present a new challenge. To care for them is becoming a great burden, financially. Can anything be done to relieve the strain? Medical research, not yet very consciously, is struggling with the question. It has no settled answer. When such questions were first raised fifteen years ago, we were not yet ready to weigh them. Now the response may become, is indeed becoming, more intelligent. The old hospitals built for infectious diseases will no longer serve. In part they are improperly constructed for these purposes. And from the point of view of research, the new situation calls for new orientation. It is still inescapable that research in infectious diseases continue here and elsewhere. Here because there is still tuberculosis, syphilis, poliomyelitis and other infections of the nervous system, rheumatic fever and influenza, elsewhere, in the tropics, because of diseases indigenous there, but perhaps transplantable here. But since the dawn of that era in which we have spent our lives, the emphasis has been almost exclusively on diseases of this kind. It would be incorrect to say that diseases longer drawn out at older ages had been neglected—cancer for example or cardiac diseases. But it is certain that in comparison with infectious diseases, they have been much less cared for and studied. The great desideratum now, is to turn increasing attention to these conditions. If they were better understood, it might become possible to manage them better. If they were better treated, expensive care in homes and in institutions might be less necessary, if they were less expensively treated, the burden of taxation



might diminish. The net result would accrue vastly to the sufferers themselves—in increased health, in greater freedom spent outside of institutions, in greater economic self-sufficiency. Psychologically, the lives of older men and women might be re-made if we learned how to make them self-sufficient to a degree impossible now, through a new orientation to employment, utilizing opportunities for activity appropriate to the aged. Embedded in the matrix of our society, no better fate is provided for them or envisaged than progressive deterioration

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I have been speaking of *what* we study. I come now to speak of *how* we do so. After long reflection and practical experience there has come to be general comprehension of the purposes and methods of the sciences in general. By the same token, a similar statement can be made of medical science. But in some subtle way, there is tacit agreement that the two are in essence somehow different. Whether they are, depends I think upon the aspect from which this judgment is made. They do not differ, there would be general agreement, in attitude to natural phenomena, nor do they differ in the seriousness with which the problems of diseases are studied, nor do they differ in the methods which both, or all, use. To recognize and to point out differences is not invidious, no more is intended than to understand a complicated situation.

Two suggest themselves—first, one having to do with the nature of the subject matter—and second, one having to do with the circumstances conditioning the activities of students of diseases. The former difference, in subject matter, has, I venture to believe, a certain validity<sup>4</sup>, the second, I think, not. To begin with, though it is not my intention to become involved merely in words, it is well to make clear the meaning I ascribe to certain terms.

Science, very briefly, is a way of looking at nature, in so far as that is possible, exactly. Two aspects are involved—the natural phenomena themselves, and a way of looking.

Research is procedure. Research represents the effort men make to

<sup>4</sup> It is perhaps a superficial experience but one to which large numbers of persons are sensitive, that in a very general sense, diseases are ugly, repellant, offensive. These are not qualities which characterize phenomena studied in other sciences. The reverse may, and often is true. It is of course a fact that to many men, perhaps especially to physicians, this aspect of diseases is without meaning. It may be that to them the very fact of ugliness has the value of attractiveness. Nor need this be regarded as odd. The last word on the subject of ugliness has not been uttered—in sight, sound, or form.

increase their comprehension. To discover what is true about anything is an arduous undertaking because, at the outset, so many things seem possibly correct. That is why research is an adventure.

The object of the whole enterprise is to *describe* nature.<sup>5</sup> At first it seems wise, at all events it seems to have been universally customary, to describe natural phenomena so as to group them. That makes description easier because there result fewer descriptions. Classification is what this phase of the undertaking is called. Sometimes, especially in our day, there lurks unfortunately, something invidious in the remark that an investigator is merely "describing." Descriptions must naturally be exact. Exactness can in fact be exhibited, purely and deliberately, without quantitative expression, in descriptions of things as they occur in nature, rough and in the whole. Men who have carried on this phase of natural enquiry have been known as naturalists or, at a stage more organized, more complicated, systematists. Hippocrates, Pliny, Linnaeus, Sydenham, Darwin, Lyell, Audubon, Wheeler, form such a group. Their very names are proof that nothing derogatory attaches to their interests or their methods. Without labors like theirs, there can be no natural science. Without them we should be talking of phoenixes, unicorns and other mythological animals. It is an evidence of the literalness of the culture of the Greeks that, unlike Egyptians or Orientals, they entered little into nature faking. The objects of concern to scientists have been natural objects. Later—and later may be taken to have a chronological meaning, though it may have also a logical one—when the *experimental era* began in its modern form, reliance came to be placed, not by any means exclusively but accompanied by a certain glamor which obscured the relations among methods, on the experimental method. A powerful agent for extending knowledge became available. The experimental method involves the conception that comprehension of a thing, of a phenomenon, can be furthered powerfully by dissecting it, by pulling it apart, by measuring and by weighing and by counting.<sup>6</sup> I need not dwell on, what

<sup>5</sup> There are those to whom action appears a more impressive and compelling motive than description. The object of the enterprise would then be to accomplish an end. The difference may be essential but it may also be a difference in emphasis. If astronomy began in the interests of action, it has remained a means to satisfy mere curiosity, or—is it perhaps to return to its original function?

<sup>6</sup> It needs scarcely to be pointed out that what is called synthesis, as in the preparation of chemical substances, dyes for example, or aromatic compounds, or in metallurgy when new alloys are made or in technical procedures or advances in general, is an extension merely of the analytical process.

is universally known, the extraordinary and unbelievable success of the method. By it Galilei, Harvey, Newton, Young, Lavoisier, their modern equally great successors and an enormous host of followers have enriched modern thought, modern knowledge and modern life.

When the experimental era began in its modern form, the temptation was great to believe that, once the parts were known, the whole would be comprehended. It was another way of thinking that the whole is equal to the sum of the parts. But doubt began to assail thinkers that matters were not so simple. It was the same situation that confronted the King's horses and the King's men when they tried, after his great fall, to put Humpty Dumpty together again. The attempt did not work. Because it did not and because in a very widespread manner there is current conviction that it cannot, the idea has been put forward by S. Alexander, Lloyd Morgan, A. N. Whitehead and General Smuts that, in putting things together again after they have been taken apart, something new becomes ingredient, something not in the constituent elements. It is, to use a crude example, as if  $2 + 2$  did not quite equal 4—that to attain 4, something not in the synthesizer's hands or mind, entered into the new composition. The doctrine that something new occurs has come to be known as emergent evolution. In speaking of analysis and research, it is unnecessary to lay undue emphasis on the imperfections of the analytical process, but it is desirable to be alive to their existence so as to avoid the disappointments which otherwise are almost inescapable. There have in point of fact been a goodly number. Leaving aside the emergence of new qualities, a phase after all of synthesis, the delays which have taken place in the cures of infectious diseases, like tuberculosis, like typhoid fever, like poliomyelitis, after the discovery and identification of the agents that help to occasion them, are known to everybody.

The whole adventure, classification and analysis, is science. I said it had two aspects, the natural phenomena themselves and a way of looking. Of the way of looking, there has just been discussion. Of the natural phenomena, there is something to say concerning a significant difference between medical and other natural sciences, the difference to which I wished to direct attention and which I wish briefly to weigh. It is the *enduring interest* that attaches to other natural sciences in contrast with the medical ones. Consider such interests as the origin of species, the origin of astronomical systems, matter, heat, electricity, the formation of the earth, light, heredity. These are concerns as little influenced as

may be by time and place. There was never a time when they did not engage serious intellectual attention, they do so now, there is good reason to believe they will continue to do so. These phenomena awoke and continue to awake enduring interests because they are enduring objects.

Turn next to the situation in the study of diseases. I have been dwelling on enduringness in interest in the objects of natural science because the objects studied in these sciences are themselves enduring. Now diseases, whether of plants or of animals, no matter what their nature, are statistically something extra.<sup>7</sup> They are occurrences which, in subtle or coarse ways, change the usual behavior of living things. The organisms are said to suffer—hence the use of the word, in the British sense, pathology. Beside being something extra, their becoming established in a society is not permanent. They change with time, they change with locality. The sweating sickness is gone. How long poliomyelitis may have existed is not known. Diseases devastating in the tropics do not exist in the temperate zones. In other cases, like rheumatic fever, the reverse may be true. Diseases may continue to turn out to be transient sojourners. By paying a necessary price, there are diseases of which we can rid ourselves—syphilis for example, perhaps scarlet fever, no doubt a number of others. Diseases, furthermore, have no independent existence, they are recognized when they have transformed the nature of their hosts, plant or animal, temporarily or permanently.

If, as I have been surmising, enduringness is a characteristic of things which have become constituted objects of study in natural sciences, it seems apparent that diseases do not partake of that quality. That is clearly the case in infectious diseases. Nor in all probability do chemical diseases, of which the deficiency states are examples, pellagra, pernicious anemia, rickets, and scurvy. Another group of diseases of great importance may be designated physiological. Physiology may be termed the study of the living behavior of an organism, as different from its mere structure. In the study of diseases, the physiology of an animal has importance because it occupies a place like the study of metallurgy in the mechanism of a steam engine. But a disease is not merely quantitatively changed physiology. A disease is something over and above and therefore

<sup>7</sup> Extra—not anticipated in a state of 'health'. I do not mean that process 'a' is joined to organism 'b' and that a + b constitute a disease. In this sense a would be what has been called an entity—an "ens". That is far from my meaning. "Extra" describes the whole organism, exhibiting phenomena, not counted as occurring in health. Health itself is a statistical conception.

different from this. The place of physiology in this scheme must not be confused. Physiology undertakes the analysis of something, animal or plant, reasonably long enduring in a species or a genus—the circulation, reproduction, digestion. These are mechanisms which are neither temporary nor local. There are of course physiological derangements which are usually called diseases, eclampsia being an example or perhaps a certain variety of arterial hypertension, or fibrillation of the auricles of the heart, or psychogenic hyperthyroidism. And a special case is that of senescence—the aging through which we all pass. My case as to enduringness is naturally not as clear-cut in respect to physiological occurrences as the distinction I have drawn suggests. Evolution and the disappearance of species and genera see to that. But there is enough of background for this distinction to occasion the social consequence in which can be perceived, implications of great importance to the position the study of medicine occupies.<sup>8</sup>

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I wish now to examine the use of another word. The word “*empiricism*” provides an opportunity for examining certain ideas and procedures commonly employed in natural science. When a certain amount of animadversion is intended in the use of the word, the adjective “crude” is prefixed. This phrase “crude empiricism” has been used especially with reference to the study of diseases, the assumption being that the study of diseases is something apart, in fact, from other studies of natural phenomena—something perhaps a little backward. On more careful reflection it becomes clear that “crude empiricism” is a phrase universally applicable to a level of discovery at which, what is called “thinking” has not been much employed or cannot be, either in the existing state of knowledge or by the individuals who indulge in that occupation. Now, when what is called “crude empiricism” is exhibited,

<sup>8</sup> There is a point of view from which contributions to general knowledge result from the study of ephemeral phenomena or from acquaintance with transient experience. Contributions so derived can, no doubt, exert significant influence in developing insights, conceptions and procedures which come much later to fruition. Broad intellectual streams can originate in obscure rills. But there remains nevertheless a value which endures, as a method of characterization, can be made to possess. Even so as a characteristic, it is unnecessary to assume that it has more than relative value. Were diseases dependent on a relation to bacteria wholly to disappear, bacteriology, for example, having received its great stimulus from this association, may be expected to remain an important interest nevertheless, because of the growing place it is coming to occupy in agriculture and elsewhere.

the subject matter under investigation is relatively in a raw native state and the means which are used to analyze that subject matter are not, in comparison with what is possible elsewhere, or in some other discipline, of a sort to be called refined. An example in medicine is the use of quinine in malaria, before an insight into the nature of malaria or the composition of quinine was obtained. Syphilis and mercury is another example, or dropsy and digitalis. In physical science, telephony and the nature of electricity, though a very rough analogue, may serve as example. The form in which I have stated this situation suggests its meaning. When something is done or some interference with a system is undertaken, as in the examples just given, it is in the natural organized state of the material, the crude, native state, in which the operation is performed. There exists no guide, furthermore, to suggest what form the operation should take. If malaria is not known to be protozoal in origin, or if it is unknown that the infecting agent is susceptible to quinine, but a therapeutic attempt is made, none-the-less—that attempt is empirical and may be termed crude. That it should be so is in the nature of things. If the object is to understand—anything whatever, a beginning must be (or is) made. Once a beginning is made, successive efforts at understanding, if on the road to success, become less and less “crude.” In the case of matter, electricity, energy, methods of analysis have now become so refined that it is evident how long a distance has been travelled from rubbing cat’s fur on amber (electron). The more we analyze, the further investigation becomes removed from crudity. Because analysis has taken place in successive simple stages, because, covering the heart of a phenomenon, there are layers of impenetrability, like the layers of petals covering the heart of an artichoke, Sherrington was moved to say, because that is the way an experimenter must look at the world, behind each mechanism is hidden another mechanism. Obviously the metaphor of the artichoke is imperfect—there is a last layer of leaves, small and apparently confused in arrangement, and then the heart. But in the phenomena to which scientists devote themselves, who knows when the last petal has been plucked and the heart of a natural process uncovered? There is a chance here (and the man who knows how to take it is the artist in science) that for *an* object, it is unnecessary—no, destructive in fact, to go further than a certain point—the point being the emergent level for which search was being made. Protection against pneumonia will not, by way of illustration, be solved at the atomic level. If the

appropriate level is passed, the nature of the thing sought may elude one's grasp Hawthorne's story of the birthmark and beauty tells the story of the devastation wrought by a perfectionist

Whether knowledge is empirical depends often on the standpoint of the critic A molecule, a protein molecule, may seem very refined in comparison with a man, but to an electron it looks enormously complex The whole business is relative

The point about empiricism and crudeness requires no further laboring It must be apparent that at the beginning nothing else than crudeness is possible Later on more insight may have been gained, but the term still be applicable Were the case of causation simple, as it is not, it would be possible to prescribe how a situation must be analyzed and possible to prophesy the results There is little confidence nowadays that that can be the situation anywhere Further understanding depends therefore on trial and error in the choice of analytical techniques Since that is inescapable all scientific analysis is crude and all knowledge empirical The only point of view from which empirical knowledge is less crude depends on the amount of relevant research that has been made Much more has become known about malaria and syphilis, about quinine and mercury, about dropsy and digitalis, about energy and electrons But to him who confronts a choice of the next step, the situation contains elements of crudity which he recognizes as not far removed from that of that predecessor of his, who took the adventurous first step So long as there are further steps there is adventure and so long as there is adventure there is crudity Otherwise research would be a commonplace procession along the avenues of the known The Lindberghs would be the last to underestimate the Nungessers

He who tells us we must halt a research until analysis has proceeded further must be certain of a number of matters around which this discussion has taken place He must know that further analysis of a complex situation is rewarding A chemist preparing therapeutic agents will appreciate this point Suppose it were optochin he had prepared and were told that too frequently giving his preparation caused blindness Against pneumococci his agent worked admirably—that was his original objective To perfect his agent and to safeguard it against unexpected, unfortunate consequences, what must he do? Must he search for other substances, similar in structure, must he try another group of agents, or must he, by analyzing optochin further, hope to discover what is offending in

the structure of his drug at a different lower level of organization?

Quinine and quinidine afford another example. The auricles, the entrance chambers in the hearts of human beings, often lose their custom of orderly contraction and do what we call, fibrillate—a state in which they live and act but do so in a very disorderly fashion. A sufferer from this disorder once noticed that frequently when he took quinine, the normal behavior of his heart was restored. He narrated his experience to his physician in Vienna, Professor Wenckebach. Professor Wenckebach sought to repeat his patient's attempts but met with scant success—and told this story in one of his treatises. It occurred to another physician—Frey—to try more or less systematically other chemical substances with which quinine is related. At this point it becomes necessary, perhaps unwarrantedly, to assume certain biographical details. Was that a rational procedure of Frey's—was there good reason to think other quinine-like substances would work better than quinine, if so, which one, related how to quinine? Or should he explore other substances—not quinine but substances belonging to that series? Or should he attempt to build up quinine into a drug more complex? Or should he break it down to find what in quinine actually worked in Professor Wenckebach's patient—purify the drug in short? Or should he look for a substance which, in Professor Wenckebach's patient, aided quinine but was absent in his own? Or did his own patient harbor a substance which interfered with the action of quinine? All these were possibilities. A complete account of how Frey behaved in this situation is unknown—it usually is. He may have tried none of these or many. He had a single guide only. He was told quinine worked in a *single* person. We are speaking of levels of organization. The only point of immediate concern is whether he should have analyzed further to find a simpler substance. It may be, he should have done so, for the result of his labors has been effective in about 60 per cent only of patients. In that sense the problem is still open and the various choices enumerated for investigation still available. What Frey did was to explore what is possible on the very level of organization of quinine sulphate. He found in the group a substance which worked 60 per cent of the time, quinidine sulphate, identical with quinine sulphate except for its action on polarized light. This was turned left—quinine turns it right. The structural formula symbolizes the difference in that the two are written as mirror images of each other. In this case, no further analytical procedures were undertaken. Success, partial, it is



true, came on a level of organization no different from before. There was no way of knowing beforehand that this would be the case. Attention to causation would not have helped. It was not known, it is not known now, what causally is essential in this reaction. It is therefore unprofitable to search for it.

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It is in the nature of things that students of any phenomenon must have first-hand knowledge of that phenomenon itself. For simple description first-hand acquaintance is all that is requisite. For analysis it is essential in addition, to possess knowledge of the art and practice of appropriate forms of analysis. There is no fundamental difference in the nature of these procedures for students of diseases and for other natural scientists. Nor is there a difference in the operations which the mind undertakes. The intellectual powers appropriate to elucidation of the two are the same, whether the object of study is a disease or an electron. The physical methods employed in laboratories naturally differ and are especially adapted to the objectives and material being analyzed. But the mind proceeds always in the same way, it knows few tricks and these few it employs indifferently wherever it has use for them. The mental act, when it comes to procedure, measures, indifferent to rational objective, length or volume or frequency. The behavior of the mind remains always the same irrespective of the tools it causes to be used in the various situations in which it acts—it describes, it classifies, it dissects. Experience must come first and then the analysis of that experience, whatever the object.

But a potential difference exists nevertheless. The practice of medicine is an ancient calling. It is as intricate as it is ancient. It is one of the nicest of the arts. Its practitioners have been in the habit of performing many social functions. These have been so absorbing that until almost contemporary time neither leisure nor opportunity nor perhaps desire was available to proceed beyond simple description, of which there has been much, to analysis\* which has but recently, and let us hope not tentatively, begun. What needs appreciating is that the gap between practice and analyzing is by way of being bridged. The existence of the gap cannot be ignored. Of its deterring effect much has been made—in my judgment much too much. When students were inadequately, or not at all, trained

\* Not psycho analysis

for research, more weight attached to the exclusive demands of practice than now. Much has changed, not least the estimate placed on traditional knowledge and on practical legerdemain, though medical opinion still insists upon transmitting a great deal of this in formal education. But in spite of all change, of persons interested in diseases, two types can be seen to emerge, one interested in advancing knowledge about them, and the other in treating them. The difference is similar to that between engineers and physicists. Physicians who wish to learn how to analyze, now can do so—and do so to extraordinarily useful purpose. But there is the difficulty I have mentioned—the gap. It is real and it is important. It occasions a difference not found, I fancy to the same extent, in other sciences having both theoretical and practical phases. Who would suppose, for example, that Graves' disease (exophthalmic goiter), in order properly to be comprehended requires knowledge of physiological occurrences and chemical processes, obviously not necessarily within the competent knowledge of conscientious practitioners of medicine? Or in the kind of cardiac affection common in older individuals, of insight into and control of the most intimate behavior of muscle fibers? And not only that, but knowledge of what underlies the behavior of those muscle fibers and their ability to carry on work. I have spoken of other difficulties which beset physicians, but here is a major one. To treat what is so obviously wrong, he must have learned, in physiology and physics and chemistry, what a man can learn only, if he learn it at all, as the result of the expenditure of all his energy. Research, in these circumstances, was at an impasse. For twenty-five years and more the effort has been made to bridge this gap by providing opportunity for a few physicians at least, to free themselves from the demands of practice. The divorce of research from demands so continuously absorbing has accomplished noteworthy results. Whether the divorce is adequate has not, I think, received sufficient scrutiny.

This much can be said safely, that time for research has been gained. And this in addition that to concentrate effort, a certain amount of irrelevant information may be left at the wayside. And finally this, that physicians who observe the phenomena of diseases receive from their intimate contact with patients and their ailments, stimuli to ferret out the meaning of what they observe. No one else has access to that knowledge. Having that knowledge and requisite training, the hope is still entertained that physicians, specially chosen, can solve the relevant

problems. It would be idle to underrate the difficulties. They do not so much consist in translating problems from bedside to laboratory as from transvaluing one pattern of knowledge with its technical (clinical) apparatus to another quite different pattern with equally exacting, if not more complicated, technical (mechanical) apparatus. To recognize, for example, a cardiac disease, to think of its origin, to study its future, is obviously a different enterprise from search for the mechanism of the contraction of muscle on which its clinical manifestations depend. For that search involves far away knowledge of proteins and the part they play in the complex structure of muscle, as a result of which they contract. Other illustrations may be chosen—syphilis for example, its dependence on a microorganism—a spirochete—and the susceptibility of spirochetes to poisoning by arsenical compounds. Or still another, diabetes mellitus, depending essentially on destruction or malfunction of a single structure in the pancreas—the islands of Langerhans—and its remediability on a substance extracted from these islands.

This discussion and these illustrations should suffice to define a peculiar situation in medical science. I have already spoken of a special characteristic of the subject matter of “medicine”—the absence of “enduringness” exhibited by diseases. And now I have added illustrations dealing with the apparently wide interval between diseases as natural phenomena and the cumbersome traditional technique for learning about them, the practical aspects of this study, on the one hand, and the equipment necessary to deal with the analytical procedures necessary in research, on the other, to explain how the position of medical science and of medical scientists has come to be somewhat different from that in other sciences and how the intellectual position of medical scientists has been regarded as differing from that of other scientists.

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It is, I think, impossible just now to exaggerate from a public point of view the importance of treatment. The motives which have brought great funds for study into existence have not, except in connection with great dangers, arisen from general public interest. The year 1776 was remarkable, aside from having witnessed the signature of the Declaration of Independence, for the effort Johann Peter Frank made, on behalf of the Archbishop of Speyer, to gather information on a social, political, or at all events on a grand scale, concerning the health of a population, so as to make this more secure. That adventure began an epoch. Usually,

it has been the illness of a friend or a member of a family that stimulated the insistent interest of private philanthropists. The universities had no funds. Government took a minimum interest only.

Once, when I defined medicine as the study of *diseases*, Doctor Thayer objected vigorously because in his judgment, joined inseparably to the study of diseases was the need to get on with the business of curing these diseases. The term medicine, he thought, included both. Obviously a term can mean whatever we say that it does. There is no reason against the use of the term "medicine" in the manner on which Doctor Thayer insisted. It is preferable though, I think, not to make the meaning of terms too inclusive, that is a way of obscuring the variety of aspects which a situation can be made to disclose. It is undoubted, indeed in the world of medicine, the notion is widespread, that to search out the nature of diseases is one of our chief obligations. But there is no doubt also, that the notion of curing diseases is universally believed to be a function of physicians. The function of medicine in the *cure* of diseases is so deeply imbedded in both public and professional minds that there have been periods of impatience with the belief that the business of curing is difficult and complicated (Hahnemann, etc.), with those who insisted on an education more or less elaborate for men whose office it might become to search out cures. Joining the search for knowledge of diseases with curing has, I think, tended to obscure the problems presented by both. It is not without importance to point out that to make cures provides, within properly defined limits, for a kind of activity not encountered in other disciplines.

Cures are of two kinds—we have depended on what I have been calling "crude empiricism" for one of them. Here there is no use for the refinement of analytical procedures. Agents not rationally related to complaints are used to mitigate them. Such agents do turn up, as digitalis in the case of dropsy, suggested by a Shropshire housewife who interested the willing Doctor Withering in her experiences, or when, owing to faith in the providence of God, the notion is entertained that where diseases occur, there in close proximity are their cures to be found—as salicylic acid (the willow) in the case of rheumatic fever.

The other kind of cure relies on nothing so simple, nothing so fortuitous. In this case cures are conceived possible because of a belief that there exists something in a morbid condition, central to it, a knowledge of which would further the possibility of cure, as of microorganisms in

typhoid fever, or of toxins in diphtheria, or excess activity of an organ, as in thyroid hyperactivity, or deficiency in a secretion, as in pernicious anemia, or defect or destruction in tissues or organs, exerting either immediate or remote consequences, as the effect on the heart in beri-beri, or of the late result of rheumatic fever, or, following in the footsteps of Ponce de Leon, substances which neutralize the action of agents that make the body age

But how are such substances to be found? There must be no mistake, they are actually and feverishly being sought. The sciences of chemotherapy, physico-therapy, immunology, pharmacology, the founding of institutes for the study of cancer and for this, that or the other, are evidence of the liveliness of the quest. Sometimes the direction of research is simple enough—the agents being already well known, in the case of hemolytic streptococcus infections, sulphanilamide, in tetanus, tetanus antitoxin, in the failure of cardiac muscle, digitalis. But in the case of cancer the situation is different, since neither cause nor cure is known, shall the search be for an agent to combat a virus or some other substance or for the correction of a constitutional arrangement responsible for the licentious growth? The direction which the search is to take is often the subject of sharp cleavages of opinion. The single subject, cancer, illustrates how in the process of analysis, talents, equipments, trainings of different forms may become serviceable. If you believe cancer is caused by a virus you want men to search for it who are perhaps differently endowed and certainly differently equipped from men who believe the solution of this problem lies in discovering a chemical substance to be neutralized, responsible for its origin or development.

To a choice of means, beside haphazard, there is no other guide but reason. But reason operates in the domain of causation and its tool is logic informed by insight, which in an exact sense is experience in action. Now, as has long been evident, reason alone is inadequate. Hope resides in the use of reason to limit the region of investigation so that then, within narrow, indeed within the narrowest framework possible, systematic trial and error can be attempted. If science is empiric, somehow experience provides it with a pattern. That is Aristotelian. Here is the inescapable region for the display of scholarship, ingenuity, resource. What the issue is to be, in seeking the cause or cure of cancer, no one now, I presume, would be bold enough to declare. It is a fortunate circumstance that men of many minds, everywhere, are engaged in this

search. But the point to be made is that once the method of crude empiricism is abandoned, the alternative, which is analysis, requires technical education not at the disposal of everyone interested in a subject. The problem is the problem of the physician as scientist. Special training is the price of analysis and analysis is the consequence of the failure of the obvious.

I could have drawn this lesson on rational therapeutics from another source. It has been said, and said plentifully, that the dawning interest in ailments of the aging is the result of social pressure. Formerly that pressure was exercised, as now in the case of poliomyelitis, to secure protection from bacterial diseases, because they, often being contagious, were dangerous and required quarantine. Comparable pressure is being exercised now because the ailments incident to older age are long drawn out and tend to be costly—indeed very costly. The study of statistics created awareness of this situation, deaths from certain causes were increasing. In the course of a few years a general conception of what this meant began to be clear—or clearer. Little was known. The study of aging began then in a more serious fashion.

The problem what and how to study is not, in some respects, unlike that in cancer. What causes aging? Is it necessary or preventable? If preventable, does it result from subtle injuries inflicted in the course of ordinary living—injuries due to infection or diet or to other environmental moments? Where is evidence to be sought? In changes in the arteries or in some other tissue or organ? Is its cause a substance secreted within the organism—constituting a master reaction—not by design, though that is not an unusual conception, but because of its fortuitous and unavoidable nature? If aging is the result of any of these causes, obviously means to bring the process to a standstill can conceivably be found. But if it should turn out that it is none of these or none comparable to them, that aging is universal, it will be necessary to turn to the notion that aging takes place in the nature of things, that somehow it is incident to living, an expression of the togetherness of the organism, not a follow the leader mechanism, that the disabilities and ailments to which it gives rise call for alleviation of disability and suffering, different—or perhaps not different—from those that are sought on the assumption of preventability.

From the point of view of research, the meaning is clear. The resources of intelligence are wanted badly in this situation—natural

historians, statisticians, morphologists, chemists of several sorts, physiologists, physicians. There may be short cuts to discoveries in this category, but the history of science does not encourage us to expect to find one. It is more likely that in order to learn what to do, it is necessary *first* to search out the forces that are at work, and the *precise forms* they assume. Attempts to anticipate solutions by short cuts have too often been futile. We are, naturally, not told that enough is known to make a solution possible. And then it is no longer believed widely that genius can advance far beyond current knowledge. Newton, for example, is unthinkable as a contemporary of Aristotle. Failure in scientific research is often the natural answer to premature adventure. The frequency of simultaneous discoveries is evidence for the correctness of this view. Pressing on the door of the unknown is nowadays constantly taking place. But we do not believe we know beforehand who will force an entrance. We believe, therefore, in freedom of research—one of the academic freedoms which ought accordingly, sedulously to be preserved. Whether a research can be made to pay is a matter of judgment. Who has this judgment? Experience counts of course, though the inexperienced, like Parsifal, often see the light. But Aristotle, Harvey, Young, Helmholtz, Pasteur, Hering, Ludwig, Gaskell, Darwin, to name only biologists, were not inexperienced. Since chance enters the calculation, there is little room for dogma.

\* \* \* \*

The clinic has been an integral part in the scheme for providing for the care and study of patients and their ailments. The very fact that clinics present the opportunity of seeing and comparing the manifestations exhibited by patients has facilitated greatly, as Shryock has pointed out, the description and classification of diseases. To be able to do this is, as we now know, indispensable in the development of scientific knowledge. When the stage of analyzing the appearances of diseases is reached, the equipment possible to clinics is essential. Equipment includes, for example, laboratories for chemical analyses, for the study of the physiological and physical aspects of diseases, for bacteriology, serology, immunity, hematology. In the past 100 years, but more especially in the past thirty, such opportunities have actually been provided on a fair scale. It has become possible for physicians to study whatever phase of a disease seems important. *Naturally clinics do not neglect the management of patients.* On the contrary. They exist for the sole purpose of encouraging

better and proper treatment, as adequate as contemporary knowledge permits. It is illuminating to observe how quickly the general public has learned to find its way to university clinics in the belief that the latest information on the cure of diseases is to be found there, where the search for their causes and nature is actively going on. The fear, once entertained, that patients dread examinations by students and are unwilling to subject themselves to novel procedures even though undertaken with proper precautions has been found not to exist or to have been much exaggerated. How to carry on clinical research is one of the lessons which has been learned.

Now, what can be successfully undertaken in the way of research in clinics depends on several factors. It is obvious that the subjects for research are diseases which the patients in a clinic present—these being presumably representative of the forms of illness present in a community. Certain illnesses can be profitably studied—others not. It would for example have been futile for Borelli or for von Helmont in the Seventeenth and Eighteenth centuries to study infectious diseases. Underlying and contributory knowledge was not yet available.

In the choice of subjects, what I have been calling the level of organization counts—and counts heavily. A distinguished biologist of the past generation spoke often to his friends of the uselessness of investigating diseases until more was known about the behavior of cells, the ultimate proximate constituents composing animals and plants. In certain directions his view was undoubtedly sound. But sera, like those used successfully in treating certain pneumonias or in diphtheria, or a drug like quinidine, or bacteria as causes of diseases, or fibrillation of the auricles as underlying a striking disorder of the heart beat—all these can be, have been, and are being studied to the great benefit of man without carrying on the investigation at a level of organization much below that on which the going concern which is the organism, carries on. It goes without saying that every analysis occurs on a level simpler than that of the thing analyzed. That is in the inescapable nature of analysis. But how far below? I have been saying, not very far, because relevant knowledge is usually not available—and in the solution of a problem, a level too far below may cease to be relevant. In analyzing morbid processes, the opportunity should be available to carry on an investigation at that level precisely, where an experienced or an especially gifted person decides it may be profitable.



Objection is raised on occasion to affording this opportunity in clinics, the point being that that opportunity should be sought elsewhere either because elsewhere the cost, financially, may be less, or because the inclusion elsewhere of that research may be more appropriate, or because historically there is value in returning that study at the locus of its origin. But this is a workaday world, it is difficult to get things done anywhere, men carry on, each his own business and do that with difficulty and against odds. Answers are sought because they are needed. Pathological anatomists, for example, are often in despair because of the lacunae, of great importance to them, left by anatomists. The situation is exactly similar when clinicians require information not supplied by physiologists. But even if anatomists and physiologists have developed a subject, there can be no obligation upon them to go on with it. They may not be aware of the need of a next step. To those to whom taking it is necessary, it is scant comfort to know where preliminary investigations were carried on, if they are no longer being housed there. The fructification of ideas cannot be shackled to a building or even to a locality. But even if the study of a subject is duplicated, the loss is usually not great. Identity in result is rare, mutual criticism is profitable, slight differences in procedure are desirable.

There must of course be some sort of common sense on what is investigated in clinics, no one now would regard it as sensible to establish a laboratory for the study of electrons. But such researches as on the metabolism of bacteria, on nomograms describing acid-base and other equilibria, the location and behavior of salts and water, the mechanism of respiratory ferments and no doubt a host of others seem to be appropriate. To afford hospitality in clinics for such studies seems wholly reasonable. So will domiciling other activities, when the principles involved are scrutinized and understood, such as describing long drawn out diseases and senescent states, especially when the interest in them is peculiar to the clinic, and the emphasis necessarily different from that outside.

The question finally arises as to whether men exist in clinics willing to devote themselves to investigations at fundamental levels. Though enterprises at such levels are relatively new, it appears already that little or no difficulty is being experienced. If there is difficulty it exists perhaps in the temptation to draw to too practical purposes, the labors of those who should be studying at simpler levels. But if so-called fundamental

researches are fostered, there exists the possibility of guiding them within pragmatic limits, and of acquainting clinicians with the value of such enterprises. Against the cost, if the cost is high, must be balanced the motives, the interest in, the concern for the subject. It seems too theoretical to expel from clinics what can be done there profitably, especially when a clinical interest meets with no outside echo. There are things, it seems, more expensive than money.

The discussion on the nature of the medical clinic has not, I believe, these many years past, given due place to these more general aspects of its life. Primary attention was focussed on practice and on teaching because they seemed to be more urgent. These three, teaching, practice and research can, of course, be conducted as coordinate functions. The devotion to practice and to teaching must in no sense be whittled away. But it will not be, if the experience of recent years is a guide. What is wanted is a realization that in university clinics, all scholars need not be cut according to the same pattern. Traditionally the roles of teacher and practitioner have been emphasized—perhaps overemphasized. But a clinic affords opportunity for the display of diverse talents, there can be doubt no longer that men of diverse talents can find happiness and opportunity there. To arrive at the precise specifications should not, within this framework, be too difficult. If the conviction begins to prevail that these various functions should find their home there, their adjustment and accommodation may safely be left to the slow, one would hope not too slow, processes of time.

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The crucial point appears to be that, to succeed, research in medicine must be regarded a serious undertaking. For whatever reasons, the issues are now regarded as sufficiently urgent by the general public, so that government is devoting increasing attention to the health of the community. To take this problem seriously means that scholars in medicine must be permitted to be serious, as are those in other callings. Education and the equipment for research must of course be adequate. And the rewards for service must be ample. Free and frequent criticism must be cultivated. This has been sharp in a technological sense. *Experimental nonsense is not lightly tolerated.* From a more general point of view—that dealing with the purposes and direction of research, criticism seems to be less well informed. Criticism of a kind can be found in presidential addresses, but the vigor, insight and fearlessness displayed is perhaps not

sufficiently incisive

\* \* \* \*

This is what I understand the meaning of medical research to be. The study of diseases has been separated in a category somewhat different from that of the other sciences. That has been due in part to the nature of its subject matter, being in a limited sense, less enduring than that taken for analysis in the other sciences. It has been due in part also to the lateness with which analytical methods have been employed in the study of diseases. The use of them now is in full swing but, being new, the education of men eager to employ them has not been adequately conceived to this end. For this reason also, a critical approach to the analysis of diseases has not yet fully evolved.

Of the objects of human interest, diseases are far from the least. The need for getting on with the understanding of many maladies is urgent. These are very varied, and require for their elucidation professional insight and equipment of a high order. The problems are becoming not less, but more intricate, the more the methods of empiricism change from crude to less crude. The meaning of medical research is to understand the mechanisms at play and to be concerned with their alleviation and cure.

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## PROCEEDINGS OF ACADEMY MEETINGS

### STATED MEETINGS

APRIL 8—*The New York Academy of Medicine Executive Session*—a] Reading of the minutes ¶ The thirteenth Hermann Michael Biggs Memorial Lecture delivered by Thomas M Rivers, Director of the Rockefeller Hospital, on Virus Diseases—twentieth century version on the *De Novo* origin of infectious agents and its significance in relation to the control of disease b] Report on election of members

APRIL 21—*The Harvey Society (in affiliation with The New York Academy of Medicine)* The seventh Harvey Lecture, The Chemistry and Biology of Male Sex Hormones, F C Koch, Professor of Biochemistry, the University of Chicago

### SECTION MEETINGS

APRIL 1—*Surgery* Reading of the minutes ¶ Presentation of cases—a] Three cases of enlargement of the lip due to hyperplasia of the submucous salivary glands, Herbert Conway, Discussion by Jerome Webster, b] Simultaneous perforation of two peptic ulcers treated by primary

gastic resection, Concomitant acute appendicitis and perforated gastric ulcer Secondary duodenal ulcer two years later, gastric resection, Myron A Sillick, Discussion by Richard Lewisohn, c] Hygroma of the neck, two years post-operative, William Klein, Discussion by John M Hanford ¶ Papers of the evening—Symposium on postoperative complications—a] Postoperative thrombosis and embolism, Frederic W Bincroft, Discussion by Margaret Stanley-Brown, b] Postoperative cystitis, Frank C Hamm, Brooklyn (by invitation), Discussion by Nathaniel P Rathbun, c] Postoperative pulmonary complications at the Roosevelt Hospital A ten year report, Lewis S Booth (by invitation), Discussion by Paul M Wood ¶ General discussion ¶ Executive session—Nomination of section officers and one member of Advisory Committee

APRIL 5—*Dermatology and Syphilology* Reading of the minutes ¶ Presentation of cases—a] City Hospital, b] New York Hospital and Cornell Medical College, c] Miscellaneous cases ¶ Discussion of selected cases ¶ Executive session—Nomination of section officers and one member of Advisory Committee

Examination of patients is limited to members and their guests

**APRIL 12—Neurology and Psychiatry** Reading of the minutes ¶ Papers of the evening—*a*] The mechanism of referred anginal pain, Heyman R Miller, Discussed by L Vosburgh Ivons, Frank Pike (by invitation), Robert H Hulsev *b*] The use of sodium chloride and hypertonic intravenous saline in the treatment of disturbed patients, Karl M Bowman (by invitation), Sylvan Keiser (by invitation) Discussed by Foster Kennedy Samuel B Wortis, S F Jelliffe *c*] Aspects of the physiology of thought and emotion with related case presentations of lobectomy and lobotomy, Richard M Brickner, Discussed by Frederick Ilneev, Israel S Wechsler ¶ General discussion ¶ Executive session—Nominations of section officers and one member of Advisory Committee

**APRIL 14—Pediatrics** Symposium on acute rheumatic fever Case reports, Lewis Stevenson, Lucy Porter Sutton, Homer Swift ¶ Panel discussion—Charles Hendee Smith, *Chairman*, Ann G Kuttner (by invitation), Currier McEwen, Irving Roth, Lucy Porter Sutton, Homer Swift, May Wilson ¶ Executive session—Nomination of section officers and one member of Advisory Committee

**APRIL 15—Orthopedic Surgery** Executive session—*a*] Reading of the minutes, *b*] Nomination of section officers and one member of Advisory Committee ¶ Papers of the evening—*a*] Some observations of a group of 1935 interior polyomyelitis patients, Charlton Wallace, *b*] A comparative study of shoulder arthrodesis and transplantation of the trapezius, Leo Mayer *c*] Parastrigular arthrodesis, Frederick Lee Liebolt (New York Orthopedic Hospital) (by invitation), *d*] Echinococcus cyst of the femur Report of a case treated by excision and implantation of bone chips, 1932-1938, M Beckett Howorth ¶ General discussion

**APRIL 18—Ophthalmology** Instructional hour—Glaucoma, Algernon B Reese ¶ Slit lamp demonstration, Milton L Berliner, Wendell L Hughes, Girolamo Bonaccolto, Gordon M Bruce ¶ Executive session—*a*] Reading of the minutes (8-30), *b*] Nomination of section officers and one member of Advisory Committee ¶ Presentation of cases—*a*] Two cases of unilateral retinitis pigmentosa, Sigmund A Agitston *b*] Demonstration of microscopic structure of coloboma of the optic nerve and macula, David Wexler, Murray Last, *c*] Two cases of malignant neoplasm of the eyelid, Maynard Wheeler *d*] Case of Von Hippel's disease (angioma of retinae), Benjamin C Rosenthal (by invitation) ¶ Paper of the evening—Operations for orbital filling, John M Wheeler

**APRIL 19—Medicine** Reading of the minutes ¶ Papers of the evening—*a*] The clinical aspects, prophylaxis, and treatment of acute anterior polyomyelitis, Josephine B Neil Discussion by S D Kramer (by invitation), *b*] Immunological aspects and treatment of meningitis, Emanuel Appelbaum Discussion by Henry Wirt Jielson (by invitation) *c*] Prophylactic and therapeutic value of convalescent serums in measles and scarlet fever, William Thalhimer Discussion by Irving Klein (by invitation) ¶ Executive session—Nomination of section officers and one member of Advisory Committee

**APRIL 20—Genito-Urinary Surgery** Executive session—*a*] Reading of the minutes *b*] Nomination of section officers and one member of Advisory Committee ¶ Presentation of cases—*a*] The injection therapy of hydrocele and spermatocele, Arthur H Milbert (by invitation) *b*] The endocrines and spermatogenesis, Robert S Hotchkiss (by invitation) ¶ Paper of the evening—The use of male sex hormone in all types of hypogonadism, Samuel A Vest Baltimore (by invitation) ¶ General discussion—Opened by Irving H Pardee

APRIL 20—*Otolaryngology* Reading of the minutes ¶ Papers of the evening—1] Plastic surgery in the deviated nose, Albert A Cinelli, 2] The management of sinus malignancies, Mervin C Merverson, 3] Diseases of the maxillary sinus and their relationship to the oral cavity, John M Lore, 4] Psychiatric therapy in dysphonia—aphonia, psychophonia—sthenia, falsetto (Slides-Recordings), James S Greene ¶ General discussion ¶ Executive session—Nomination of section officers and one member of Advisory Committee

APRIL 26—*Obstetrics and gynecology* Executive session—Nomination of section officers and one member of Advisory Committee ¶ Paper of the evening—Sterility causes, methods of investigation, and treatment (illustrated by a motion picture in color), Samuel L Siegler (by invitation) Discussion by Raphael Kurzrok, Robert S Hotchkiss (by invitation), Isidor C Rubin, Francis W Sovak

#### AFFILIATED SOCIETIES

APRIL 18—*The New York Roentgen Society* (in affiliation with *The New York Academy of Medicine*) Case reports—a] interesting cases, b] A case of ostecephaly, Joseph E J King (by invitation) ¶ Paper of the evening—A qualitative-quantitative concept of radiation therapy, William H Meyer, Discussion by Ralph F Herendeen, John R Carty, Edith H Qumbly, M A (by invitation), Arthur Mutscheller, Ph D (by invitation) ¶ Executive session

APRIL 20—*New York Section of the Society for Experimental Biology and Medicine at The New York Academy of Medicine* The longevity of the mammalian erythrocyte, Albert S Gordon, William Klemberg (Introduced by Harry A Charrier) ¶ Identification of the porphyrin compound found in cultures of *C diphtheriae* and *Mycobacteria*, Calvin B Coulter, Florence M Stone (by invitation) ¶ The effect of the pulse on lymph formation and interstitial movement of substances, Robert J Parsons (by invitation), Philip D McMaster ¶ Curative effect of vitamin B<sub>1</sub> and the vitamin B<sub>2</sub> complex on experimental hyperthyroidism, Victor A Drill (Introduced by Ralph H Cheney) ¶ Decreased choline-esterase activity of serum in jaundice and in biliary diseases, William Antopol, Arthur Schiffman (by invitation), Lester Luchman (by invitation) ¶ Movement of water against a gradient in models, W J V Osterhout, J W Murray (by invitation) ¶ Business session

APRIL 28—*New York Pathological Society* in affiliation with *The New York Academy of Medicine* Case reports—a] Primary carcinoma of the nail, James R Lisa, Jacob Levine, b] Tuberculous sclerosis with cerebellar involvement and colloid cyst of the septum lucidum, Amour F Liber ¶ Papers of the evening—1] A consideration of certain types of benign tumors of the placenta, Andrew J Marchetti (by invitation), 2] The passage of substances through tissues and the formation of lymph, Robert J Parsons (by invitation), Philip McMaster (by invitation) ¶ Executive session



BULLETIN OF  
THE NEW YORK ACADEMY  
OF MEDICINE



JUNE 1938

TRANSFERS OF WATER AND SOLUTES  
IN THE BODY

*Harvey Lecture January 20, 1938*

JOHN P PETERS

John Slade Ely Professor of Medicine Yale University School of Medicine

PROPERLY KNOWLEDGE of the processes by which water and solutes are transferred in the body begins with the discovery of the circulation of the blood by the great physiological pioneer from whom this society proudly derives its name. This aspect of the subject, however, will receive no attention this evening. The movements of water between the blood stream and the interstitial fluids and the important functions of the lymphatic system will also be neglected, since they have been subjects of recent lectures of Eugene M. Landis<sup>1</sup> and Cecil K. Drinker, respectively. I shall confine myself entirely to the discussion of the processes which control the motions of water and solutes between cells and the fluids in which they lie. Even in this connection the effects on these movements of changes in the reactions of the blood and body fluids, which have been so admirably elucidated by Dr. Van Slyke, will receive only scant consideration. Since, as Van Slyke has shown, the effects of pH changes derive from alterations of the osmotic pressure relations between media, they represent only a special case of one

part of the subject of this lecture History must also largely go by the boards to permit adequate presentation of recent experimental work and its implications My position here tonight is chiefly that of recorder or reporter of investigations that have been carried out over a period of years in my laboratory by a number of persons whose names will appear as the story unfolds Relevant material from other sources will be mentioned without any attempt to treat the literature exhaustively

First I should like to consider certain experiments dealing with the composition of the red blood cell and its behavior in its native extracellular or interstitial fluid, the blood plasma The red blood cell lends itself to study because it can be isolated for examination and because its metabolic processes are quite slow and can be brought practically to a standstill by moderate chilling There is much evidence to prove that the contents of the red blood cells have the same osmotic pressure as blood serum and are in osmotic equilibrium with the latter This means that, in spite of the great differences in their composition, both cells and serum contain the same concentrations of osmotically active chemical components The differentiation is brought about, apparently, by the fact that the membrane of the cell has a highly selective permeability It is quite freely permeable to water If blood is diluted with water this water distributes itself between cells and serum in the same proportion as the water which was originally in these media The consequence is that the cells swell and, if enough water is added, will ultimately burst Urea and certain other simple organic compounds also penetrate the cell membrane quite freely Consequently solutions of urea, although they have a definite osmotic pressure, act exactly like water Furthermore, urea added to serum does not alter the size or composition of the blood cells To proteins the cells are quite impermeable, otherwise hemoglobin could escape into the serum The molecular concentration of protein in the red cells is more than three times as great as that in the plasma *A priori* it might be expected that the osmotic pressure of the cellular contents would be far greater than that of serum It is a similar difference in concentration of protein between plasma and interstitial fluids that, according to the Starling theory, balances the hydrostatic force of the blood pressure and retains fluids in the blood stream In the equilibrium between cells and serum, however, the unequal distribution of protein is compensated by impermeability to other substances, especially the cations, sodium, potassium, calcium and magnesium If red

lood cells are suspended in solutions of sodium chloride of varying strength it will be found that they retain their original size and shape in that solution which has a concentration of about 0.9 per cent NaCl, or approximately 150 millimolar. Since NaCl in solutions of this strength is almost completely dissociated into  $\text{Na}^+$  and  $\text{Cl}^-$  ions, the solution contains 300 osmotically active milliequivalents. Cells behave in this solution, however, quite differently than they do in a 300 millimolar sea solution. In the latter they swell as they would in so much water. They do not swell in the sodium chloride solution because the sodium is unable to cross the cell membrane. In sodium chloride solutions stronger than 150 millimolar the cells shrink, in weaker solutions they swell. The degree of expansion or contraction depends on the concentration of salt which is added. Equilibrium is reached in each case when enough water has been transferred across the cellular membrane to equalize the concentrations of active osmotic solutes on the two sides of the membrane.

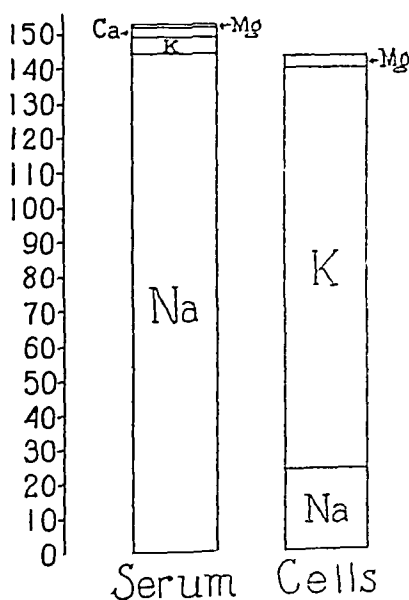


Fig 1—The average molar concentrations of base in human serum and red blood cells

After these few preliminary remarks I should like to present certain data and experimental results. Fig 1 shows the concentration of anions

and cations in normal serum, not as they are usually given, in relation to units of volume, but as osmotic equivalents (millimols) per liter of water. These data are from analyses made by Miss Pauline Hald.<sup>3</sup> The total concentration of base in serum water, 153 millimols, is approximately the same as that of an isotonic salt solution, 150 millimols. For purposes of calculation, then, it should be possible to use the concentration of base in serum as a measure of the effective osmotic pressure of the serum, that is, of the components of serum which cannot cross the cell membrane and which, therefore, will determine the distribution of water between cells and serum. If this is true and if the cell membrane is completely impervious to base, it should follow that, when water or salts or both are added to blood, the concentrations of base in the serum before and after the addition should vary inversely as the volumes of water in the cells

$$\frac{Bs_1}{Bs_2} \text{ should equal } \frac{Wc_2}{Wc_1}$$

Where B represents mols of base per kilo of water, W kilos of water, the subscripts s and c, serum and cells, and 1 and 2 the bloods before and after treatment, respectively. It will be apparent from the figures in Table I that experimental results conform to expectation with surprising accuracy. In these fourteen experiments, performed by Wakeman, Eisenman and Hald,<sup>4,5</sup> the ratios of base and of cell water are almost identical in the great majority of instances, although water, and the sulfates, carbonates and chlorides of both sodium and potassium were added to blood. Since then similar results have been obtained with phosphates of sodium and potassium. These and other experiments of a like nature can leave no doubt that human red blood cells under the conditions of these experiments are quite impermeable to the bases, sodium, potassium, calcium and magnesium, and that, when the concentrations of base in the serum are changed, the cells give up or take on water in such proportions that the osmotic pressures in the two media always remain identical. Fig. 2, from data of Klinghoffer,<sup>6</sup> shows that solutions of urea (marked by circles) and of glycerol (the triangles) have the same effect as so much water (crosses), proving that these substances enter the cells with perfect freedom. Sucrose is unable to enter the cells, therefore in solutions of this sugar red cells behave as they do in salt solutions.

Glucose presents a rather particular case. It has been demonstrated

TABLE I

Relations of Transfers of Water between Cells and Serum to Changes of Serum Base after Addition to Blood in Vitro of Salts or Water

Experiment No *	$\frac{W_{c1}}{W_{c2}}$ (1)	$\frac{B_{s1}}{B_{s2}}$ (2)	(1)/(2)	Added to blood
1	0.800	0.798	1.00	147 m eq $\text{NaCl}$ and $\text{KCl}$
4	0.849	0.825	1.03	313 "
5	0.817	0.821	1.00	322 " $\text{KCl}$
2	0.928	0.912	0.99	92 " $\text{Na}_2\text{SO}_4$ and $\text{K}_2\text{CO}_3$
3	0.869	0.938	0.93	139 " "
6	0.906	0.907	1.00	129 " $\text{Na}_2\text{CO}_3$
7	1.334	1.293	1.03	250 cc $\text{H}_2\text{O}$
8	1.260	1.305	0.97	270 "
1-a	0.934	0.926	1.01	115 m eq $\text{K}_2\text{CO}_3$
2-a	0.865	0.757	1.14	356 " $\text{KCl}$
3-a	0.816	0.779	1.05	357 " $\text{NaCl}$
4-a	1.189	1.268	0.94	200 cc $\text{H}_2\text{O}$
5-a	1.230	1.322	0.93	250 "
6-a	0.871	0.882	0.99	197 m eq $\text{Na}_2\text{CO}_3$
Average			1.001	

Experiments 1 to 8 are from Winkler, Eisenman and Peters,<sup>4</sup> the remainder from Eisenman, Hald and Peters<sup>5</sup>

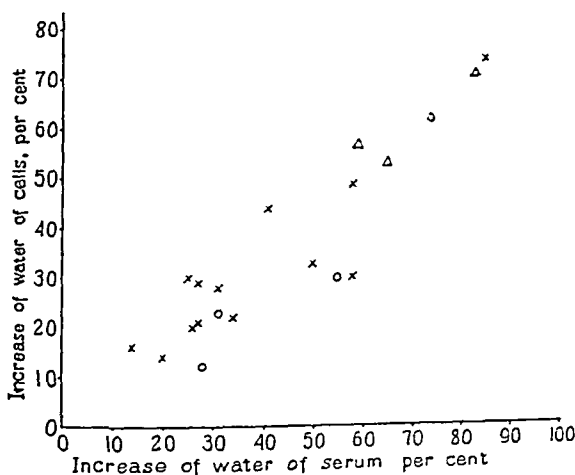


Fig 2—Per cent increases in water of cells and serum after the addition to blood of water X, urea solutions o, and glycerol solutions Δ

repeatedly that in human blood glucose is equally distributed through the water of cells and serum. The addition to blood of dilute solutions of glucose causes cells to swell as they do in water, the glucose and water distributing themselves equally between the two media. In stronger glucose solutions cells do not swell so much, taking up less than their share of glucose. The factors that limit the load of glucose which the cells will assume are not yet clear. Klinghoffer has, however, shown, in some unpublished experiments, that, in spite of this discrepancy in the distribution of the glucose, osmotic equilibrium between cells and serum is still maintained—that is, water and glucose cross the cell membrane in equal proportions, the transfer of water being conditioned by the transfer of glucose. It should be mentioned that the conditions under which glucose is not evenly distributed in human blood are not encountered in life.

With this much established it became necessary to learn whether red blood cells behave in the same manner while they are in circulation in the body. With this end in view Eisenman and Hald<sup>5</sup> examined blood of patients before, and at intervals after, injections of large quantities of hypertonic sodium chloride or sodium sulfate. In these experiments (see Table II) the base of serum increased from 6 to 27 millimols between the two observations, which were made, in two instances, at intervals of as much as eighteen hours. In every experiment except the ones surrounded by the black line, in which a single analysis was probably in error, the ratios of cell water and of serum base agree quite as well as they did in the *in vitro* experiments. It would seem, then, that both in the test tube and in the body the red blood cells respond to changes in the concentration of base in the serum as if they were quite impermeable to base, adjusting osmotic equilibrium by transfers of water alone. As far as their size and water content are concerned, then, these cells would seem to be entirely at the mercy of the serum in which they are bathed.

In early experiments *in vitro*, in which whole blood and serum were investigated by Wakeman and Eisenman<sup>4</sup> it was also proved by direct analysis that no base passed into or out of the cells. This has since been confirmed with more exact techniques by Eisenman and Hald.<sup>5</sup> To our great concern however, when the same techniques were applied to the *in vivo* experiments unmistakable changes in the base of cells were detected. The two series of experiments are contrasted in Table III. The calculated limit of error in the estimation of  $Bc_2 - Bc_1$ , is 4 millimols, an

TABLE II

*Transfers of cell water in relation to changes of serum base*

Experiment	(1) $\frac{W_c}{W_{ct}}$	(2) $\frac{B_{st}}{B_{st}}$	(1) (2)
M	89.3	91.7	0.94
T 1-2*	100.0	83.6	1.20
1-3*	96.6	85.9	1.12
2-3	104.7	102.7	1.02
Bo	93.3	96.2	0.97
Be	96.0	97.0	0.97
Cr	93.2	95.8	0.96
Ch	95.3	96.2	0.99
S	94.2	94.8	0.99
Tr	98.7	94.3	1.05
		Average *	0.99

\* Experiments T 1-2 and I 1-3 are excluded

TABLE III

*Transfers of base between cells and serum*

Exp	In vivo			Exp	In vitro		
	(1) $B_{ct}$	(2) $B_{ct}$	(2)-(1)		(1) $B_{st}$	(2) $B_{st}$	(2)-(1)
M	97.4	101.3	3.9	1	100.5	101.3	0.8
T 2-3	96.6	87.7	-8.9	2	101.3	105.3	4.0
Bo	98.6	86.3	-12.3	3	117.8	116.7	-1.1
Be	111.7	105.1	-6.6	4	112.3	110.4	-1.9
Cr	101.4	113.5	12.1	5	112.8	113.7	0.9
Ch	107.6	102.2	-5.4				
S	104.9	93.4	-11.5				
Tr	106.6	107.5	0.9				

estimation that seems to be supported by the *in vitro* experiments. Nevertheless this was exceeded in five of the eight *in vivo* experiments, the very experiments in which changes of cell water and analyses of serum gave no evidence of transfer of base. A paradox therefore presented itself.

To find the source of this paradox it is necessary to turn to more direct consideration of the composition of the cells. By reference to Fig. 1 which compares the average molar concentrations of bases per unit of water in serum and cells, it may be seen that there is slightly more total base in serum. In addition the base of serum is overwhelmingly composed of sodium, while in the cells potassium predominates. The concentrations of total base in the two media are, on the whole, sufficiently alike, to

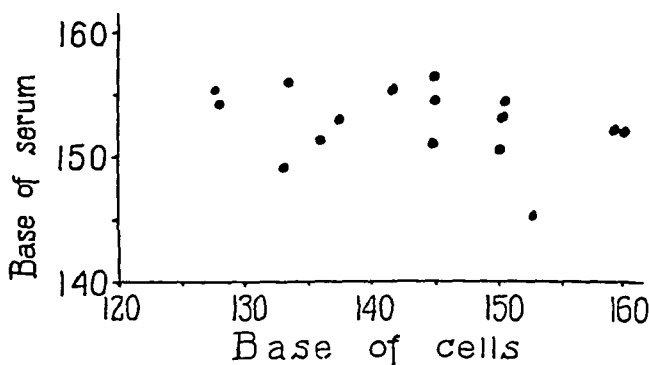


Fig 3—Comparison of base in water of cells and serum of human blood

give the impression that, in the cells as in serum, inorganic salts are chiefly responsible for the osmotic pressure. Since the osmotic pressure of both media is the same, the concentrations of base in cells and serum should vary directly. That this is not the case is quite evident from Fig 3, in which the base of serum is plotted against the base of cells. It is obvious that serum base varies within relatively narrow limits, cell base varies over a much larger range. Furthermore there is no demonstrable relation between the two. At one end of the scale the ratio of cell base to serum base is 0.86, at the other end, 1.05. If these figures are to be accepted potassium and sodium cannot have as important an osmotic role in cells as they do in serum. Osmotic equilibrium can exist when the concentration of base is distinctly higher in the cells than in the serum. In this case, presumably, a fraction of the base in the cells must be osmotically inactive (perhaps because it exists in non-ionized form) or else the serum must contain some unusual unrecognized components. The latter is the less probable explanation, since the composition of serum is simpler and more uniform than that of cells. In those instances where base is far lower in cells than serum, it must be supposed that other chemical substances in cells are bearing more than their usual share of the osmotic load. Regardless of the explanation, unless the analyses are incorrect—and this possibility has been abandoned after exhaustive examination of the methods—it appears that any variation of base in serum is attended by a proportional change of osmotic pressure, whereas the base of cells can vary within wide limits without affecting osmotic pressure.

At first sight this conclusion seems absurd because it is so much at variance with traditional teaching. Emphasis has, in the past, been placed



on the average concentrations of base in cells and serum which, as you saw in the slide a short while back, are nearly the same. Variations in individual bloods were attributed to errors. It was to eliminate this excuse that Miss Hald<sup>7</sup> perfected the techniques by which these analyses were made. On the face of it the results before you are less absurd chemically and biologically than the old concepts. In serum salts make up the major portion of the solutes, and in such a simple medium, may be expected to be quite completely ionized and active. Osmotic comparisons with salt solutions and chemical comparisons with natural and artificial transudates, moreover, have demonstrated that serum meets these expectations. The contents of the cells are far more complex and contain many substances which do not exist in serum, but which must contribute to the osmotic pressure. Moreover, in these cells metabolic processes are causing continuous permutations and combinations of solutes. Complex compounds are breaking down and being again reconstituted in a perpetual cycle. Were there not some mechanism by which these reactions could be, so to speak, osmotically buffered, they would produce constant—sometimes large—changes in volume and water content of the cells. How, if these occur, have they escaped observation? There is adequate precedent for variation of the osmotic activity of base in the combinations of calcium with protein in serum. There must, in addition, be some means by which cells can, in times of need, accumulate stores of material without being forced to take on at the same time excessive amounts of water. The aggregation of glucose into large molecules of glycogen is an example of a reaction that must serve just this purpose. Finally, this cell can not be so utterly impervious to base as our osmotic experiments would indicate or it would be forever deprived of some of the elements that are essential for its vital activities. It remains, then, to discover the mysteries of the facultative permeability of the cell.

In an attempt to learn the significance of the changes of serum phosphate that accompany rapid movements of glucose in the body, it seemed highly advantageous to use whole blood for analyses rather than serum. It had been rather generally assumed that the red blood cell membrane was freely permeable to inorganic phosphate. When Dr. Lena Halpern<sup>8</sup> investigated the subject, this proved not to be the case. The distribution of inorganic phosphate between cells and serum is quite capricious and does not change when potassium and sodium phosphates are added to blood.

And now I should like to make a slight diversion. In all the *in vitro* experiments on permeability that have been mentioned special efforts were made to prevent intracellular activities. Blood was treated anaerobically and kept cool. If exchange of gases is prevented blood can be kept at ordinary refrigerator temperatures for from twelve to twenty-four hours without appreciable change, at room temperature for from two to four hours. If it is warmed to body temperature glucose in the cells is oxidized, organic phosphate esters are broken down to inorganic phosphate and lactic acid is formed. These reactions can be modified by exposure to oxygen or  $\text{CO}_2$  and can be reversed by the addition of glucose. Dr. Halpern found that during the glycolytic process inorganic phosphate passed out of the red cells into serum. The process by which it escaped was not merely diffusion, since phosphate was transferred to serum even when its concentration in the latter had been greatly increased by the addition of inorganic phosphate. The escape of phosphate did not denote injury of the cells because the direction of the flow of phosphate could be reversed by the addition of the glucose. It remains only to add that Hald found that potassium accompanied phosphate across the membrane. It can be inferred from these experiments that the red blood cell is always in osmotic equilibrium with its environmental fluid, the blood serum, and responds by changes of volume and exchanges of water to alterations of the concentration of base in serum. As long as it is in the resting state, moreover, its membrane remains impermeable to the bases, to phosphate, to sulfate, but during metabolic activity base and phosphate pass in one direction or another, presumably in accordance with the needs of the cell. These transfers are not accomplished by a mere process of diffusion and must therefore involve chemical reactions.

To demonstrate such exchanges in the body and to measure their osmotic effects has proved more difficult. In the test tube glycolytic processes are accompanied by changes of blood pH,  $\text{CO}_2$  and oxygen that confuse the picture greatly. In life it has proved hard to induce transfers of phosphate of sufficient magnitude to cause measurable changes of osmotic pressure. After administration of insulin and glucose, in a few instances, relatively large shifts of phosphate have been demonstrated by Miss Hald and Dr. Margaret Dann.<sup>9</sup> With some reservation it may be stated that these shifts could not be correlated in direction or magnitude with the slight transfers of water which sometimes occurred. This is suggestive, but by no means conclusive, evidence that the phos-

phate and base which were transferred had little or no osmotic activity

So much time has been wasted on this red blood cell, not because of its intrinsic importance, but because it is peculiarly adapted to such investigations. Throughout it has been recognized that it might prove quite different in its reactions from other more active cells, and therefore a useless model. However, there was continually growing evidence that some of its characteristics were shared by muscle and other tissue cells. These I shall not attempt to treat historically. It has been generally assumed that between the active cells of the body and the blood vessels there is a body of fluid, the interstitial fluid, that has the composition of an ultrafiltrate of serum. Our knowledge of this fluid is entirely based on inference and information obtained in pathological conditions accompanied by transudation. In the latter it must be assumed that the transudates are merely expansions of an already existent body of fluid. If there is interstitial fluid it should have the composition of an ultrafiltrate of serum, being chiefly composed, so far as inorganic elements are concerned, of sodium and chloride. Analyses of muscle tissue by Fenn,<sup>10</sup> the Eggletons,<sup>11</sup> Eichelberger and Hastings<sup>12, 13, 14</sup> and others have proved that the proportions of chloride and sodium in muscle are much the same as those in serum and that the total quantities of these substances in muscle can be accounted for if about 20 per cent of the muscle mass consists of interstitial fluid. Furthermore, if isolated, living, resting muscle is immersed in sodium chloride solutions the salt apparently diffuses into about the same volume of the muscle. Studies by Eggleton<sup>15</sup> indicate that inorganic phosphate, also, diffuses into about the same proportion of the muscle mass. Urea, on the other hand, diffuses freely throughout all the water of the muscle.<sup>16</sup> From these experiments it would appear that there is a barrier to the free diffusion of some solutes through muscle which distinguishes about one fifth of the tissue from the other four fifths. Harrison, Darrow and Yanner<sup>17</sup> analyzed whole animals for chloride, sodium and potassium. They found that, if bone were excluded, the total quantities of sodium and chloride in the bodies of dogs, monkeys and rabbits could be accounted for if 20 to 30 per cent of the body were composed of an ultrafiltrate of serum, leaving enough potassium and magnesium to supply base for the remainder of the water in the body. It seems not unreasonable to believe, therefore, that there is extracellular fluid amounting to about one-fifth of the body weight, and that the remainder of the water in the body, within the cells, is almost, if not quite,

devoid of sodium and chloride Eichelberger and Hastings<sup>12, 13, 14</sup> have shown that this hypothesis affords an adequate explanation for the changes in the composition of muscle that are produced by injections of normal salt solution, by alkalosis and acidosis and by various dehydrating measures which alter the osmotic pressure of the serum and, therefore, cause the muscle cells to swell or shrink

To make the analogy to the red blood cell still closer, Pollack, Flock, Mason, Essex and Bollman<sup>18</sup> perfused isolated hind limbs of dogs with blood to which they added inorganic phosphate Analyses of the muscles showed that the inorganic phosphate did not diffuse into the cells, nevertheless, when glucose and insulin were added to the perfusate the concentration of phosphate esters in the muscles increased Presumably, then, under the stimulus of metabolic activities chemical processes were activated which conveyed phosphate across a cell membrane which it did not ordinarily traverse Fenn and Cobb<sup>19</sup> and Thaler<sup>20</sup> have found that potassium can be made to escape from muscle by various measures such as exercise and hemorrhage Fenn has concluded that the membrane is always permeable to base, but not to anions, and attributes these exchanges to alterations of pH, which have not always been demonstrated<sup>20</sup> It seems quite as possible that they are expressions of metabolic activities within the cells

The application of these principles to the analysis of phenomena of human physiology and pathology in a truly quantitative sense begins with Gamble's<sup>21</sup> classical studies of the salt metabolism in fasting and acidosis Although I shall not dwell on these in detail I cannot refrain from paying him tribute for the inspiration he has given to all those who have worked on problems of salt and water metabolism Gamble recognized the importance of distinguishing between extracellular and intracellular losses of water and salt and demonstrated the disasters that come from reducing the osmotic pressure of the body fluids by depleting them of salt He also demonstrated the tenacity with which osmotic pressure is maintained in the face of metabolic disorders He pointed out the intracellular segregation of potassium and the extracellular distribution of sodium and chloride, and the possibility of distinguishing by balance studies the source of losses of cations and water It was not, however, possible by the technique which he employed to allocate these cations with accuracy nor to measure directly the relative changes in volume of interstitial and cellular fluids The chief difficulty in this respect lay in

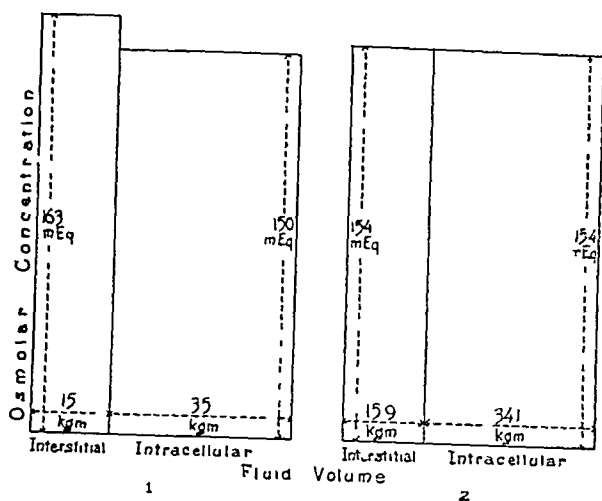


Fig. 4—The effect of adding salt to interstitial fluid

the fact that, even if sodium is entirely confined to the extracellular fluids, changes in its concentration, because they alter osmotic pressure, will disturb the distribution of water between cells and interstitial fluid. This is illustrated in Fig. 4. In the first part are shown two solutions, each containing base in a concentration of 150 millimols per liter, separated by a membrane which is pervious only to water. If enough salt is added to the smaller compartment to increase the osmolar concentration by 13 millimols, water will enter from the larger compartment until the osmolar concentration is again equalized. At this point, pictured in the second part of the figure, it will be found that, since the ultimate osmolar increment in both compartments is identical, the effect on the concentration of salt in either compartment will be the same as if the salt had diffused freely through the membrane. The volumes of the two compartments have changed, but those changes of volume cannot be detected by the usual methods of chemical examination which measure concentration only.

Theoretically this difficulty could be circumvented by a simple expedient. If, instead of one substance, two substances were used, which originally existed in plasma in different concentrations, it should be possible by simultaneous equations to determine how far they were diluted by water derived from the cells or concentrated by passage of water into the cells. The two substances chosen were sodium and chloride. I shall not tire you now with the details of the experiments which have been published by Laviertes, D'Esopo and Harrison.<sup>22</sup> Suffice it to say

that the concentrations of chloride and sodium did not differ enough to permit accurate deductions from clinically practicable procedures in any but extreme cases. The results were, however, sufficiently compatible with our premises to stimulate new endeavors.

Some method of measuring the interstitial fluids was obviously needed. Substances must be found which were not normal constituents of serum and which would pass freely through vascular walls without penetrating cells. To make a long story short, after searching the literature and considering the adventures with red blood cells, three substances were selected that seemed likely to meet requirements: sulfocyanate, which Crandall and Anderson<sup>23</sup> had shown diffused through about 20 per cent of the body, sulfate and sucrose, neither of which penetrated the red blood cell. All these substances can be quantitatively recovered in the urine, proving that they are not subjected to chemical or metabolic changes. For various reasons none proved quite ideal for the purpose for which it was intended. Sulfocyanate enters red blood cells and apparently combines to some extent with the lipoids of blood plasma, sulfate and sucrose are excreted too rapidly by the normal kidney. In addition sulfate figures must be corrected for endogenous serum sulfate as well as endogenous sulfate excretion. Nevertheless some encouraging measurements were made by Laviètes, Bourdillon and Klinghoffer.<sup>24</sup> The principle of the methods was quite simple. The test material was injected (or, in the case of sulfocyanate, sometimes ingested). After an appropriate interval samples of blood and urine were collected and analyzed for the test substance. The total amount injected minus the quantity excreted, divided by the concentration in the water of serum, will give the volume of fluid in which the material is dissolved if it is distributed through this fluid in a uniform manner. Results of certain comparisons of the distribution of the three test substances are given in Table IV. When the objections to the three substances are considered, the agreement appears highly satisfactory. It is hard to escape the conviction that there is a barrier which separates the fluids of the body in a broad way into two compartments, of which one, into which these substances chiefly or solely diffuse, makes up roughly 20 to 30 per cent of the body weight, for that is what these figures imply in terms of the total body mass.

An attempt has been made more recently by Purple and Laviètes<sup>25</sup> to utilize the same principle for the measurement of the total water of the body. For this purpose urea, because of its known universal diffusibility,

TABLE IV

*The volumes of distribution of sucrose, sulfocyanate and sulfate in the body*

Subject	Volume of distribution of		
	Sucrose liters	CNS liters	SO liters
1	18.8	18.2	
	18.3	18.4	18.7
2	18.3	19.0	
3	15.3	17.4	
4		16.6	
		17.0	18.8

seemed the most suitable test substance. However, because of the amounts of endogenous urea in the blood and the variability of endogenous urea formation and excretion and the diuretic effect of urea, it proved disappointing. In its place thio-urea was chosen. This compound possesses most of the chemical and physiological properties of urea, and is excreted completely, unchanged, in the urine. It might be considered as a labelled urea molecule. Unfortunately specific quantitative chemical methods for its detection and measurement are not highly sensitive, therefore large quantities of the compound had to be given, so large as to cause serious gastric symptoms. However, before the connection of these symptoms with the drug was established, measurements of total fluids were made on two normal persons and one patient. The volume of distribution varied from 68 to 70 per cent of the body weight, values consistent with accepted conceptions of the water content of the body. Attempts are now being made to refine the analytical technique so that the method may be made clinically feasible.

Meanwhile, since the experiments with sulfocyanate, sucrose and sulfate gave reason to believe that sulfate did not enter cells, it occurred to Bourdillon and Lavietes<sup>26</sup> that the distribution of sodium could be traced more accurately if it were injected in the form of sodium sulfate, earmarking the exogenous sodium ions, so to speak. Large quantities of hypertonic sodium sulfate were, therefore, injected into normal subjects. Blood serum before and after the injections was analyzed for sulfate, chloride, bicarbonate, base or sodium, and protein. In addition oxygen capacity and cell volume of whole blood were measured, and urine was analyzed for potassium, sodium, chloride and sulfate. Finally sodium sul-

TABLE V

*Intravenous injection of 102 m eq of  $\text{Na}_2\text{SO}_4$  and 250 cc  $\text{H}_2\text{O}$* 

	1	2	2-1	2/1
Serum $\text{SO}_4$	0.5	15.3	+14.8	
B	148.8	154.5	+5.7	
Cl	98.5	93.1	-5.4	105.8
Distribution volume of				
CNS	16.2	17.1	+0.9	105.5
$\text{SO}_4$	—	12.9		
Change of B estimated from Cl		140.5	+14.0	
Interstitial fluid change from B and $\text{SO}_4$				106.5

focyanate was given in advance of the experiments to serve as a check upon the volume of the interstitial fluid. Time was not given for the sulfate to become completely distributed because this would have permitted the excretion of too much of the salt. The results of one such experiment are shown in Table V. The first column represents conditions before the injection, the second column after the injection, the third column the changes in the blood as the result of the injection, and the last column the ratio of the final volume of the interstitial fluid to the initial volume, estimated by a variety of methods. The quantities of sodium, sulfate and water retained are calculated from the amounts given, corrected for the quantities excreted in the urine. At first sight it might be anticipated that, since equal quantities of the two ions were injected and equal quantities were excreted, the concentrations of base and sulfate in serum would increase to the same extent. Actually sodium rose only 5.7 milliequivalents, while sulfate rose 14.8 milliequivalents. If however, attention is turned to chloride, it is seen that this fell 5.4 milliequivalents, although negligible amounts of chloride appeared in the urine. It would appear, then, that the body of fluid containing chloride was diluted to the extent shown in the last column, 5.8 per cent. Comparison of the sulfocyanate figures indicates that the volume of the interstitial fluid increased from 16.2 to 17.1 liters, a difference of 0.9 liters or 5.5 per cent. If it be assumed that sodium was restricted to the same body of fluid, the sodium originally in this fluid must have been diluted just as much as the chloride. At the end of the injection it should have fallen from its original concentration of 148.8 to 140.5. If this value, which is placed between the first two columns, is subtracted from the final figure 154.5



the actual increment of exogenous sodium is found to be 140 milli-equivalents, an extremely satisfactory agreement with the 148 milli-equivalent increment of sulfate. If it be assumed that the increments of base and sulfate were identical it can be estimated from the changes of sulfate and sodium that the interstitial fluids expanded 65 per cent. The data are, then, entirely compatible with the theory that sulfate, chloride, sodium and sulfocyanate were distributed over an identical fraction of the total water in the body and that this fraction, approximately one twentieth of the body mass, increased in volume by about 1 liter. If it did expand to this extent some of the extra water must have been acquired from other parts of the body, because the volume added by the infusion, when corrected for that excreted in the urine, amounted to only about 200 cc. The simplest explanation of the facts, in view of other evidence that has been adduced, would seem to be that the sodium sulfate entered only the extracellular fluids. Because it increased the osmotic pressure of these fluids water was withdrawn from the cells to restore osmotic equilibrium. It is possible to calculate that, if this was the case, the cellular fluid volume was about twice as large as the extracellular. This experiment is one of those in which it was earlier shown that the red cells contracted in proportion to the increase of base in the serum, about 4 per cent. The estimated contraction of the tissue cells falls somewhat short of this, which is to be expected since comparison of sulfate and sulfocyanate distributions in column 2 shows that the adjustments occasioned by the injections of salt had not yet come to equilibrium. This is only one of the most complete of a consistent series of experiments by Bourdillon and Lavietes.<sup>26</sup>

In general, then, tissue cells appear to resemble red blood cells in their behavior. There is some evidence that sodium may be more completely excluded from the tissue cells and that these cells are almost, if not quite, devoid of chloride. Furthermore, these two ions are effectively excluded from the cells. When the concentration of sodium in the interstitial fluid changes, osmotic equilibrium is restored by transfers of water to or from the cells without transfers of base. No evidence has been adduced that base is admitted to or discharged from the cells in behalf of osmotic equilibrium *per se*. If these inferences are justified the maintenance of the osmotic integrity of the interstitial fluids should be of prime importance to the function of the cells, which must imbibe water and swell every time the concentration of sodium in the serum falls, or shrivel

whenever it rises. The concentration of sodium in the interstitial fluids controls, however, only the load of water in the cells, that is the dilution of the cellular constituents. The actual quantities of these constituents in the cells—or at least the inorganic components—appear to be controlled by entirely different mechanisms. The impermeability of the resting cell to potassium, phosphate and other chemical substances is an essential protective property. It is equally essential that there be some means to unlock the barrier when need arises in the cells for more of these materials or for the discharge of any excess. Apparently the key to the barrier is entrusted to the metabolic processes of the cells, thus insuring automaticity.

Although potassium is the predominant base of all cells, including the red blood cell, it is quite as impossible to drive potassium as it is to drive sodium across the membrane of the resting red blood cell. This may not be true of other cells. Bourdillon<sup>27</sup> has found that when potassium chloride is given by mouth, the potassium distributes itself through a larger volume of fluid than the chloride does, a volume that approaches the total amount of fluid in the body. It seemed possible that the potassium might be absorbed from the gut more slowly or less completely than the chloride. But, when Winkler (unpublished studies) gave potassium chloride intravenously he obtained similar results. The increments of serum potassium and chloride in these experiments, which were conducted on human subjects, are small, but the differences in the increments are consistent and unmistakably significant. Moreover, in similar experiments Bourdillon found that, after sodium chloride, increments of sodium and chloride were the same. These experiments, if they are substantiated by further work, can only mean that inorganic potassium, when it gains access to the interstitial fluids, passes freely into the cells. Since exogenous potassium is excreted quite rapidly, it must escape from the cells with the same ease. The red blood cell model at this point fails. Of course the potassium which cannot be found in the interstitial fluids may seek other repositories than the cells. To jump to this conclusion at once is quite unjustifiable. It is equally unjustifiable to assume that the mere increase of potassium in the interstitial fluid initiates some metabolic disturbance by which it is conveyed into the cell. Since the volume of distribution of the potassium approaches the total fluid of the body, the simplest hypothesis is that inorganic potassium diffuses freely across the cell membrane. In this case, the intrinsic potassium of cells, since it does not diffuse

outward, must be restrained from free diffusion by some force other than the mere impermeability of the envelope of the cell

This would not be incompatible with any of the facts thus far presented. So long as sodium is ionized and cannot gain access to the cells, changes of its concentration must control the size and water content of the cells. If inorganic potassium can diffuse freely between cells and interstitial fluid it would have no influence upon the distribution of water. This fraction of potassium is quite small. The great mass of potassium may be relatively non-ionized, combined with organic phosphate esters and protein. Presumably this would be in equilibrium with the moiety of ionized inorganic potassium and, therefore, not entirely unaffected by the concentration of the latter. Its concentration would, however, depend far more upon the material available for the formation of the compounds in which it is found, of which phosphate is presumably one of the most important components. Since phosphate can enter or leave the cell only under the stimulus of metabolic processes, movements of potassium would be conditioned by these same metabolic processes which control phosphate. All this discussion of potassium is, of course, highly speculative in comparison with the preceding discussion of sodium, which is experimentally documented. It is, however, consonant with the physiologic and pathologic data now available.

Gamble<sup>21</sup> found that in the dehydration of starvation acidosis potassium as well as sodium was wasted. This he connected first with losses of protein and glycogen from the cells. Later<sup>28, 29</sup> he discovered that potassium was sacrificed also in the diuresis evoked by acidifying salts, this time without appreciable losses of carbohydrate or protein. It seemed possible that wastage of extracellular sodium might itself provoke the discharge of potassium from the cells and that this might serve to mitigate the effects on the cells of altering the amount of salt in their environment. Nevertheless, in experiments by McCance<sup>30</sup> in which the sodium of the body was greatly depleted by withdrawal of salt from the diet combined with sweating, potassium losses were quite insignificant. In these experiments it was estimated that at least 25 to 30 per cent of the sodium and chloride in the body was withdrawn and the concentrations of these substances in the serum fell 10 to 15 millimols.

In Addison's disease and in some animals after adrenalectomy sodium wastage is accompanied by retention of potassium. This retention, according to the balance studies of Harrop and his associates,<sup>31</sup> causes no

immediate rise of serum potassium. The potassium which is retained apparently enters, or becomes imprisoned in, the cells. Harrison and Darrow,<sup>32</sup> by analyses of the tissues of rats, animals which do not waste sodium, have shown that after adrenalectomy cellular potassium increases without a comparable increase of water. If this is verified, it exemplifies the accumulation in the cells of osmotically inactive potassium. It also suggests that removal of the adrenals gives rise to a widespread derangement of cellular metabolic processes. It has been demonstrated further that adrenalectomized dogs are benefited by restriction of potassium in the diet and can be thrown into shock by the administration of potassium salts.<sup>33</sup> This is consistent with the hypothesis that the intrinsic potassium of the cells is affected by the supply of inorganic potassium in the interstitial fluid. These discoveries of the role of potassium detract in no respect from Loeb's<sup>34, 35</sup> discovery that in man and many animals absence of the adrenal cortex causes depletion of sodium and symptoms that can be relieved in whole or in part by administration of sodium salts. Harrison and Darrow's rats, in spite of the fact that they did not waste sodium spontaneously, proved more susceptible than normal rats to withdrawal of sodium. Moreover, when the sodium in their interstitial fluids fell, the tissue cells swelled, proving that they had lost none of their capacity to respond osmotically.

A recent unpublished study by Klinghoffer and Laviertes of a patient with Addison's disease may be reported with a certain amount of reserve. He proved to be on the verge of a crisis and, by the time the three-day study was completed, required cortical extract to revive him. Throughout the whole period of observation, therefore, he was sinking deeper into shock in spite of vigorous administration of saline. From Table VI it can be seen that the concentration of sodium in the serum was only slightly reduced and potassium was normal as were also chloride—and bicarbonate which does not appear in the table. Moreover, because of the vigorous therapy they did not change appreciably. There was a large positive balance of sodium and chloride and a smaller negative balance of potassium. During this period (see Table VII) the volume of the interstitial fluid, measured by sulfocyanate, rose from 20.0 to 24.7 kgm, an increase of 4.7 kgm. Estimations by means of the sodium and chloride balances indicated increases of 3.2 and 3.8 kgm respectively. The agreement is not perfect, but satisfactory enough under the circumstances. It seems reasonable to believe that the volume of the interstitial fluid in-

TABLE VI

*Sodium and potassium balances in a case of Addison's disease*

*Composition of serum water*

<i>m. eq</i>	<i>June 22</i>	<i>June 25</i>	<i>Change</i>
Sodium	141.3	140.5	-0.8
Potassium	5.1	4.7	-0.4
	—	—	—
Na + K	146.4	145.2	-1.2
<i>m. eq</i>	<i>Sodium</i>	<i>Chloride</i>	<i>Potassium</i>
Intake	1851	1659	113
Output	1395	1255	227
	—	—	—
Balance	456	404	-114

TABLE VII

*Changes in distribution of water in a case of Addison's disease*

*Interstitial fluid*

<i>kilo</i>	<i>June 22</i>	<i>June 25</i>	<i>change</i>
from SCN	20.0	24.7	+4.7
from Na	—	—	+3.2
from Cl	—	—	+3.8
	—	—	—
Conservative estimate			+3.5
Weight	73.0	74.5	+1.5
	—	—	—
Fluid received from cells			+2.0
			<i>m. eq</i>
Cellular base loss expected			250 to 300
Potassium loss observed			100
			—
Accumulation of cellular K			150 to 200

creased 3 or 4 kgm. At the same time the patient's weight increased only 1.5 kgm. Therefore the interstitial fluid received about 2 kgm. of water from the cells. But with this 2 kgm. of water only about 100 milliequivalents of potassium were lost, a far smaller amount of potassium than even the most conservative estimates would credit to this quantity of cellular water. This suggests that potassium became more concentrated in the cells. Analyses of blood (Table VIII) showed that the concentrations of potassium and potassium + sodium in the red blood cells were far higher during this crisis than they were a month or two later when

TABLE VIII

*Changes in the composition of serum  
and cells in the blood of a patient  
with Addison's disease*

*Millicquivalents per kilo of water*

	<i>June</i> <i>22</i>	<i>June</i> <i>25</i>	<i>July</i> <i>31</i>	<i>August</i> <i>12</i>
Serum				
Na	141.3	140.5	142.3	143.2
K	5.1	4.7	3.8	5.0
Na + K	146.4	145.2	146.1	148.2
Cell				
Na	20.7	31.2	27.3	15.7
K	142.5	127.2	98.2	107.6
Na + K	163.2	158.4	125.5	123.3

the patient was in excellent condition. Too much emphasis should not be placed upon these quantitations, especially those that deal with the concentrations of base in the red blood cells, because just before the patient died a few days ago in another crisis, the potassium and sodium of his red blood cells had not risen again. However, on this occasion sodium of the serum was distinctly lower. It may be of some significance that in the balance studies water and electrolytes moved in the directions that the experiments of Harrison and Darrow would lead one to anticipate.

In another series of experiments Yanner and Darrow<sup>30</sup> have shown that hyperthermia causes similar osmotically inactive accumulations of potassium in cells, but in this case the changes are restricted to the central nervous system.

Depletion of serum sodium is extremely common in clinical medicine. It is regularly encountered in the states of dehydration which result from severe vomiting, diarrhea or gastro-intestinal fistulae, in diabetic acidosis, in water intoxication, in lobar pneumonia, in terminal stages of nephritis, and sometimes with no discoverable cause. It has been too generally assumed that in all these conditions as well as Addison's disease depletion of base has the same quantitative and qualitative effects. Nevertheless, those who have compared, in any large series of patients, the concentrations of electrolytes in the serum with the physical condition, must have been impressed with the wide range of symptomatology associated with deficits of base and with the variability of the response to restoration of the concentration of salt in the serum. The dramatic condition of the

patient in the crisis of Addison's disease differs strikingly from that of the person who has lost sodium by the vomiting of pyloric stenosis, diarrhea or diabetic acidosis. Mere replacement of sodium and water in a severe crisis of Addison's disease may be little more than a futile gesture, I suspect that the administration of cortical extract in pyloric stenosis or diabetic acidosis would be equally fruitless.

In advanced nephritis the sodium of serum may become greatly reduced. Frequently such salt deficits are attended by disturbances so profound that the condition has been named "uremia from lack of salt." If the advanced nephritic is given a salt poor diet, especially if large amounts of fluid are also administered, both base and chloride of the serum will fall and the weight will usually diminish. Appetite and thirst may fail and the blood non-protein nitrogen often rises even if no more serious symptoms develop. We have reported<sup>37</sup> a nephritic who displayed this tendency to waste sodium to such an extent that when he was given as much as 15 gm. of sodium chloride daily, the chloride of the serum rose only to the upper normal limit, 105 m eq. When salt was withdrawn it fell gradually to 85 m eq., at which point the total base of the serum was only 125 m eq. That is, both sodium and chloride were almost 20 m eq. below normal, reductions quite as great as those encountered in the crises of Addison's disease. In spite of this extreme salt depletion and the hypotonicity of his serum the patient felt none the worse and exhibited none of the symptoms which commonly accompany such salt deficits. The red blood cells in this case swelled in direct proportion to the reduction of base, and from studies of the electrolyte balance it may be inferred that the tissue cells behaved similarly.<sup>22</sup> Freedom from symptoms cannot be attributed to any peculiar compensatory reaction which protected his tissues from the reduction of osmotic pressure. One peculiar feature was noted. Thirst did not flag when salt was withdrawn and the body weight varied only 2 kgm. in the course of the experiment. He did not suffer the dehydration which usually follows salt restriction in advanced nephritis.

Winkler and Crankshaw<sup>38</sup> have recently reported a series of patients with advanced pulmonary disease, especially tuberculosis, who exhibited a peculiar tendency to waste sodium and chloride in the urine and who had persistently low concentrations of these substances in the serum. The conditions could easily have been confused with Addison's disease except that salt depletion in these cases had no spectacular consequences.

Further examples of the variable effects of salt deficits could be mul-

upplied to no great advantage. If I should dare to differ from Gamble in any important respect it would be to challenge his statement that the concentration of base in the interstitial fluids is more jealously guarded than is the volume of these fluids.<sup>39</sup> Unfortunately this doctrine is one to which I so long adhered that it ill befits me to do more than confess my own error. Apparently, in this as in other matters, circumstances alter cases and it is incumbent upon us to inquire into the circumstances. The determination of concentrations of salts in the serum is a unidimensional measurement. This must be supplemented by measurements of the volumes of the fluids in which those salts are dissolved if precise information is to be secured about animals which have three-dimensional bodies. Even this does not suffice: the allocation of these fluids and solutes between the various compartments of the body cannot be neglected. Among these compartments the blood stream, the interstitial fluids and the cells must be separately considered. Although the blood serum is only part of the interstitial fluid, the shock of hemorrhage and the edema of heart disease or nephritis can leave no doubt that the distribution of fluid between the subdivisions of this general system is of great moment. Harvey's and Starling's circulations cannot be forgotten. Mere expansion of the interstitial fluid as a whole seems to cause little disturbance, but considerable reduction of its volume, even without change of composition, is not so well tolerated. Changes of its osmotic pressure (i.e., the sodium concentration) usually, but not invariably, provoke serious symptoms. Why there should be exceptions remains to be discovered. Are the untoward effects of base depletion entirely referable to changes in the volumes of the cells as has been suggested? How large a part must be attributed to the concomitant loss of interstitial fluid with which base depletion is usually associated? Do those who apparently escape evil effects escape because the volume of the circulating blood or the interstitial fluid remains relatively unaltered, or by virtue of some compensatory transfer of base or by the inactivation of previously active osmotic components of the cells? Finally, what are the processes that unlock the cellular membranes and possibly alter the osmotic activity of the cellular constituents and how can they be controlled?

It is halting first attempts at dynamic measurements of the distribution of fluids and salts and the forces that govern them which I have tried to describe tonight. Tentative inferences have been drawn of which it is hoped that some at least may survive the acid test of further investigation.



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## CANCER OF THE GASTROINTESTINAL CANAL\*

*The Bulkley Lecture*

CARL EGGERS

Professor of Clinical Surgery New York Post Graduate Medical School  
Columbia University

VITAL STATISTICS indicate that next to heart disease cancer is the most common cause of death. Constant vigilance to provide earlier diagnosis and treatment is essential if a larger number of patients are to be saved from an untimely death. One of the chief obstacles in the fight against cancer is the pessimism concerning its curability which is so prevalent among laymen as well as a great many members of the medical profession. A knowledge of actual results which are obtainable by good surgery in reasonably early cases will go far in replacing such pessimism by a healthy optimism. Educational campaigns are essential to disseminate known facts. The American Society for the Control of Cancer has set itself the task of educating the general public in the symptomatology of cancer and urging medical consultation. To educate the doctor in properly evaluating early suggestive symptoms and signs is the duty of medical organizations and institutions. Much is being done in this respect, but in spite of this, patients with untreated cancer continue to present themselves with malignant growths in such an advanced state that the tumor is irremovable and any thought of cure has to be abandoned.

In analyzing the reasons for this one may place patients into one of three groups:

(a) Those in whom the cancer comes on so insidiously that no variation from the normal is noticed until it has reached a stage of growth and dissemination which precludes surgical removal. Such cases will always occur and no amount of education can prevent them.

(b) Patients who present a history strongly suggestive of cancer and who give the examiner the very definite impression that if they had consulted a physician at the first appearance of symptoms, their lives might have been saved. This group may gradually be reduced by cancer campaigns.

(c) In the third group are included those patients who consulted a physician on the first appearance of symptoms or signs, but in whom the importance of these symptoms was not appreciated. A harmless looking or feeling lump may have been dismissed with the remark "just a little gland, as long as it does not hurt, do not bother about it." A discharge may have been treated with a douche without investigating its source. For symptoms of indigestion prolonged medicinal treatment may have been instituted instead of diagnostic tests. An x-ray examination may not even have been considered. It is this group of cases which is put squarely at the door of the doctor. It is our duty and responsibility to educate ourselves so that this group will become steadily smaller. To do so it is necessary to keep the subject constantly before the medical profession. This has been recognized by many and efforts are being made all over the country to help reduce cancer mortality by properly directed educational campaigns.

The late Dr. L. Duncan Bulkley, a distinguished member of this Academy, and a well-known dermatologist, who was intensely interested in cancer, was one of those who recognized the value of post-graduate education in this branch of medicine. He established the Bulkley Lecture at The New York Academy of Medicine in 1929 for the purpose of annually bringing some phase of this vital subject to the attention of the general practitioner.

We can tell you nothing new nor startling for the knowledge concerning cancer has been built up gradually. Many men have contributed to it until today it is manifest that the application of this knowledge saves many lives which were formerly lost.

Cancer of the gastrointestinal tract is a large subject for one lecture. It is realized that the inclusion of the esophagus, stomach, the entire intestines, especially the colon and rectum, makes it impossible to go into great detail. Nevertheless it was thought advisable to present it in this comprehensive way in order to bring out certain pertinent points concerning symptomatology, laboratory findings and treatment which are common to all parts of the canal.

The chief functions of the gastrointestinal tract are the digestion and absorption of food and the elimination of the non-used waste products. An important associated function therefore must be the regular propulsion of its contents through the canal. Any interference with this mechanism leads to disturbances which manifest themselves as

symptoms These disturbances in turn may initiate other symptoms or physical signs Carcinoma tends to narrow the lumen of the alimentary canal wherever it happens to develop This produces interference with the propulsive mechanism, hence symptoms due to some degree of disturbance of the mechanical function are the most likely This in turn leads to interference with normal secretion, absorption and elimination and initiates a symptom complex of nutritional disturbance which produces weakness and loss of weight

The entire gastrointestinal canal is about twenty-five to thirty feet in length, of which only nine to ten inches form the esophagus and a similar length the stomach Of the remainder, four-fifths form the small intestines and one-fifth the colon and rectum

The lumen of the canal varies a great deal in size and it appears that cancer is most common where it is narrow and offers opportunity for stagnation and irritation The rarity of cancer of the small intestines is explained on the theory that its fluid contents flow along a fairly uniform lumen without obstruction and irritation This theory accords with our present day conception of the etiology of cancer which seems to point to chronic irritation in a susceptible individual as the most likely cause In all locations of the gastrointestinal tract in which cancer is commonly encountered such factors can usually be adduced

In the esophagus coarse and poorly masticated food, very hot or other irritating food, may produce cell changes at the physiological narrowings In the stomach improperly masticated food, changes in secretory activity with spasm, retention and irritation may well play a role In the colon stagnation with formation of toxins and secondary irritation offer a fertile field for the development of cancer

Figures concerning the incidence of cancer vary a great deal, depending on the source, whether from clinical medical, surgical or autopsy material According to the vital statistics of New York City for 1936, cancer of the esophagus constitutes about 3.1 per cent of all cancers, cancer of the stomach 17.2 per cent, cancer of the small intestines 0.2 per cent, cancer of the colon and sigmoid 12.7 per cent and cancer of the rectum and rectosigmoid 7.2 per cent

The proportion to all cancers of the gastrointestinal tract is about 6.1 per cent in the esophagus, 33.8 per cent in the stomach, 0.4 per cent in the small intestines, 25.1 per cent in the colon and sigmoid, 14.2 per cent in the rectum and rectosigmoid

Except in the esophagus and in the anal canal, which are lined with squamous epithelium and usually give rise to epithelioma or epidermoid carcinoma, all cancers of the gastrointestinal canal are adeno-carcinomas. They arise from the columnar epithelium lining the entire tract. Though they have the same origin, there is considerable difference in the gross as well as in the microscopic appearance of these tumors. Some are small, somewhat pedunculated or polypoid, project into the lumen and do not early penetrate into the wall. Others form flat serpiginous ulcers with overhanging edges and have a great tendency to penetrate the gut wall. Still others form large bulky masses or very small scirrhus tumors. Gelatinous or mucoid degeneration may take place and still further complicate the picture. An explanation for this behavior is to be found in the normal difference of cells in the various sections of the alimentary canal, in the virulence of the cancer cells, as well as in the reaction of the host to the invasion of malignant cells.

The difference in development of cancers of the gastrointestinal tract explains some of the differences in their clinical manifestations as well as in their course and prognosis. It is known that the papillary types of tumor which project into the lumen offer a more favorable prognosis than those invading the wall and involving the peritoneal coats, and they are of a lower grade of malignancy. However it is not only the lower grade of malignancy which makes them more favorable, but the fact that they may give rise to bleeding, or if favorably situated, produce intestinal obstruction and thus become recognized before invasion of lymph nodes has taken place. The small scirrhus cancers on the other hand are frequently not recognized until very late. They give rise to no bleeding and the increasing constipation receives scant attention except an increase in the dose of a laxative until acute intestinal obstruction supervenes. Then again large massive tumors may give rise to bleeding or obstruction and in addition to that they may be palpable.

The early symptoms produced by a malignant growth are unfortunately so vague that they are difficult to recognize. If allowed to go untreated, the outstanding symptom common to nearly all cancers of the gastrointestinal tract is obstruction, but as we have just explained, this symptom may appear early or late. Thus a growth developing at a narrow portion of the canal, and projecting into the lumen may produce a mechanical obstruction and lead to recognition early. A similar growth developing in a wide portion of the canal may grow to a large size,

perhaps never lead to obstruction and become recognized chiefly because of its bulk, or because of bleeding, or breaking down with resulting toxemia or anemia

It is usually some degree of obstruction, vague though it be, which first attracts the patient's attention. Whether this obstruction is in the esophagus, the stomach, or the intestines, spasm is immediately added to the mechanical factor, and congestion with more or less stagnation results. Added to this are secretory changes, disturbed digestion and a whole train of symptoms depending on the location and extent of the lesion.

The diagnosis of early lesions depends to a large degree on the alertness and experience of the examining physician. Does he on the basis of symptoms presented suspect carcinoma? It cannot be stressed too often how important it is not to overlook what appear to be vague or unimportant symptoms such as loss of appetite, indigestion or any change in the bowel habit.

Changes in function due to some narrowing of the lumen are the most important. They may not approach actual obstruction but be sufficiently marked to temporarily delay the passage of food or intestinal contents. Depending on the location one may have discomfort or difficulty with swallowing, fullness in the stomach associated with belching, nausea and occasionally vomiting, anemia due to bleeding, absorption of retained material or products of the tumor, possibly constipation and diarrhea alternating, or difficulty with gas.

Many of these lesions being ulcerative, there may be blood, either in the vomitus or in or on the feces. It may be in small quantity detected only by chemical tests, or it may appear grossly. Chemical tests, especially gastric analysis may be helpful in determining altered secretion, products of stagnation, or blood.

At times one may be able to feel a mass, either in the stomach, colon, or rectum. The presence of a palpable tumor does not mean that it is not removable and should never act as a deterrent to operation.

One may bring a lesion into view with the aid of an esophagoscope, gastroscope or proctoscope.

By far the greatest aid in the detection of lesions of the gastrointestinal tract are roentgen examinations. This is true particularly of those cancers which are inaccessible to palpation or instrumental examination. If done with the proper technique the percentage of error is

slight Most roentgenologists have developed methods of examination which in their hands rarely fail to demonstrate an existing defect It has seemed to us that the greatest justification for criticism of procedure in the diagnosis of cancer of the gastrointestinal tract lies in the fact that roentgen examination is not resorted to sufficiently often With only slight symptoms, even though suggestive, a physician hesitates to subject a patient to the expense involved, and as a result the lesion progresses from a curable one to one less favorable The important thing to bear in mind and to teach, is to have x-ray examinations made at the first sign of trouble and not to wait until the patient presents a typical picture of advanced disease To make such examinations more easily possible for everybody may well be the goal of all those interested in Public Health Any or all of these examinations may be initiated after a good history and physical examination have made one suspect the presence of cancer One should not rest until the lesion has been found or definitely ruled out In case that is not possible, careful observation and re-examination at a later date are indicated

Treatment consists of *destruction* or *removal* of the growth Destruction is applicable only in readily accessible tumors, and may be carried out by means of radium, Roentgen rays, actual cautery or surgical diathermy In spite of the fact that some tumors are radiosensitive, radiation therapy has so far not attained the results which had been hoped for At the present time surgical removal offers the best chance for cure Only in very favorable cases may one at times carry out local removal with a satisfactory result Usually radical resection of the tumor with sufficient normal tissue surrounding it, and a portion of gut above and below the lesion, and including the lymphatic drainage area, is the operation of choice

### CANCER OF THE ESOPHAGUS

Owing to the deep situation of the esophagus, and its inaccessibility to ordinary vision or palpation, the older methods of examination were limited, and treatment likewise restricted Following the advent of the Roentgen rays and the esophagoscope, exact diagnostic methods have been developed, and the successful treatment of carcinoma has advanced considerably

Cancer of the esophagus may occur at any level, but has certain sites of election which correspond with the physiological narrowings



The onset is insidious and for this reason medical aid is rarely sought until dysphagia has become manifest. Even then, this symptom is often not given the necessary attention and the disease is allowed to progress until regurgitation of food, salivation, pain and loss of weight occur. All of these symptoms are late manifestations and explain, in part at least, why surgery for cancer of the esophagus has not made more progress.

The chief obstacle to early diagnosis is the vagueness of symptoms. One has to be mentally alert when a patient with slight difficulty during the act of deglutition presents himself. Suspecting a lesion and referring the patient to a competent roentgenologist and endoscopist momentarily ends the physician's responsibility at this point. It is better than to resort to bouginage with its attendant dangers of irritation and possibly perforation. In experienced hands the diagnosis is usually made easily by means of roentgenograms, which in a typical case show an irregular deformity with slight dilatation above it. This should be supplemented by an esophagoscopy and biopsy because errors in diagnosis are possible.

With a definitely established diagnosis the question arises as to what should be done for the patient. It is the aim of treatment to cure the disease, and if that is not possible, to relieve symptoms and prolong life. Radical operation, x-ray and radium treatment, surgical diathermy, bouginage and palliative gastrostomy may be considered. Which course to follow depends on the patient's general condition, as well as on the state of the local disease.

Palliative treatment is used in those patients who refuse radical operation or in whom the disease has progressed beyond the operable stage. Under palliative treatment the following measures may be adopted as indicated.

1 *General Medical Care* In early cases when swallowing is still possible, a well balanced diet should be arranged, with all food finely divided to prevent stagnation. Attention must be given the heart and kidneys, and bowel elimination aided. Adequate rest is of importance to preserve the patient's strength. In all advanced cases the most important consideration is the administration of adequate quantities of fluids to overcome dehydration and toxemia. One may resort to hypodermoclysis, proctoclysis, or venoclysis. The addition of 5 per cent glucose to any of these is helpful. Whether to tell the patient of the nature of his illness has to be judged in the individual case. Inasmuch as most patients

with this lesion are men, it is frequently advantageous to do so in order to gain their cooperation and to enable them to arrange their affairs. If one has the impression that such knowledge will lead to severe mental depression it may be better to withhold the information.

2 *Gastrostomy* This should not be reserved as a last resort, but be performed in most cases soon after a diagnosis has been made. Though it is a relatively simple operation which may be done under local anesthesia with a low mortality in patients in fairly good general condition, it is much more dangerous in an emaciated dehydrated individual with poor healing power. Patients frequently object to such an operation because of the annoyance of constantly wearing a tube, and the necessity of having all food administered in that way. To overcome these objections, a Janeway gastrostomy is recommended which does not require the use of a tube except at meal time and which usually does not leak. After it has been in use a short time, and the esophagus has been put at rest, the swelling due to irritation associated with the carcinoma may subside and the patient be able to swallow better than before. In all complete obstructions gastrostomy is a temporary life-saving measure.

3 *Dilatation* In some clinics this method is used in preference to others. If carefully performed by passing bougies over a previously swallowed silk thread or under guidance of the eye through an esophagoscope, there is probably not much risk connected with it in trained hands. Unless one is an expert, however, perforation with a fatal outcome may result. It gives temporary relief only.

4 *Intubation* After a carcinomatous stricture is dilated, it is at times possible to insert a tube, which maintains the lumen permanently. These tubes vary in size and are made of rubber or metal. Their introduction requires skillful manipulation and should be attempted only by experts.

5 *Radiation Therapy* Although classed with the palliative measures it is really intended to be more than that. One's aim is to destroy the tumor either by means of deep roentgen therapy or by the insertion of radium capsules or radon seeds. Unfortunately, such happy results have not been attained so far, but with the modern treatment developed at some clinics, considerable relief and probably prolongation of life may be looked for. Radiation therapy may, of course, advantageously be employed in combination with dilatation, establishment of a gastrostomy or other treatment.

6 *Electrocoagulation* In selected cases, especially those with an elevated polypoid type of tumor, destruction of the growth may at times be accomplished. One has to be very careful to select only such cases in which the growth is small and superficial, because the destructive action of the coagulation may easily lead to perforation.

Only a small group of carefully selected cases may be considered for radical operation because of the fact that a patient usually has a well advanced carcinoma when he comes under a surgeon's care and because of our present state of knowledge. Because the operation is always a formidable one, the patient should be in fair general condition and one whose symptoms and findings suggest that the lesion is in its early stages.

The surgical approach varies depending on the location of the tumor. The technical problems involved are quite varied and it is therefore best to consider the treatment under the headings of (a) carcinoma of the cervical portion, (b) carcinoma of the thoracic portion, (c) carcinoma of the lower esophagus and the cardia.

Cancer of the upper end of the esophagus is removed from above. At times the larynx and pharynx must be sacrificed because the growth has a tendency to spread into the hypopharynx. For the resulting defect a reconstruction operation may be considered later. A gastrostomy is usually advisable.

Removal of a carcinoma affecting the middle or thoracic portion of the esophagus is technically the most difficult and dangerous. Reports of successful extirpation are increasing in the literature. Ingenious methods of approach have been developed. The best known one, and the one having the largest number of successful results to its credit is the one developed by Torek. It consists of a preliminary gastrostomy, followed by a transpleural resection of the affected esophagus. The upper end is brought out at the neck and is later connected with the gastrostomy by means of a rubber esophagus. In suitable cases a reconstruction of the esophagus may be carried out. The method has lately been modified by dividing the main operation into two stages. Perhaps at the time the gastrostomy is performed, or as an independent procedure, the upper end of the esophagus is brought out at the neck through an incision along the anterior border of the sternocleidomastoid. The tumor is then removed at a later date through the thorax.

Recently there has come a report from England and another from

Germany of the successful extirpation of a carcinomatous esophagus by blunt dissection with the aid of the hands passed through a high epigastric and a neck incision along the entire mediastinum without opening the chest. The lower end is divided, the stumps closed and the entire esophagus drawn out at the neck and removed. Extrapleural resection through the posterior mediastinum has also been successfully performed.

Cancer of the lower end of the esophagus may be removed through the chest or the abdomen. The ideal operation is to reimplant the stump of the esophagus into the fundus of the stomach in order to permit normal deglutition. A gastrostomy is usually not required.

### CANCER OF THE STOMACH

According to available statistics, cancer of the stomach is responsible for at least one-third of all male and one-fifth of all female cancer deaths.

The general attitude of the profession regarding carcinoma of the stomach is one of resignation, and is no doubt based on the observation that the majority of patients come under surgical care at a time when resection of the stomach, which offers the only chance of cure, is precluded by the extent of the disease. Even a palliative operation is possible in only a comparatively small group of cases.

With the refinements in diagnosis, with better preoperative and postoperative care, and with meticulous surgery, there has been considerable improvement. Recent statistics by well-known surgeons and clinics offer a distinct note of hopefulness, which encourages one in the belief that general improvement in results may be expected. It should therefore be our aim to have patients with vague gastric symptoms referred early to a physician, to have the physician employ all his resources in making an early diagnosis, and then to have the patient promptly operated on. Even when this has been accomplished, however, a large percentage of patients will still come under observation at a time when the disease has progressed beyond the operable stage. This is due to the fact that cancer of the stomach is frequently so insidious in its onset, and the symptoms so slight that the stomach is not even suspected of being the seat of disease. In the beginning there is often no more than slight deviation from normal health. There may be just a feeling of lassitude, slight loss of appetite and lack of interest. Not until diminution of appetite and a little indigestion appear is there any suggestion

that the stomach may be at fault. As the disease progresses, loss of appetite or a distinct aversion to food, especially meat, becomes more marked, there may be definite discomfort after eating, nausea, belching or eructation. Associated with this may be anemia, loss of weight and occasional vomiting. Inasmuch as indigestion is common in middle life, which may be due to a variety of causes, and is often transitory in character, the patient does not seek medical advice until persistence or severity of symptoms compels him. For the same reasons the physician frequently does not realize the serious implications of comparatively slight symptoms. Instead of subjecting the patient to diagnostic methods which would lead to early recognition of the underlying cause, he is apt to try unduly prolonged medicinal treatment for the relief of symptoms. If we were not dealing with cancer, such a course would not be serious, but the cancer grows steadily while we procrastinate, valuable time is lost and the condition may progress from an operable to a less favorable one. There is no retracing our steps when we have missed an early diagnosis. The battle against cancer of the stomach demands that we think of it whenever a patient presents himself with slight indigestion or aggravation of an old existing indigestion. Thinking of it and feeling the necessity to prove its presence or to rule it out is the only safe guide.

Physical examination is usually negative at the beginning of the disease unless a favorably situated tumor at the pylorus causes early obstruction. In such a case a palpable tumor or a peristaltic wave passing from left to right across the epigastrium point to pyloric obstruction. Usually such findings are an indication of more advanced, but often still operable, disease.

Diagnostic measures which may be employed include a test meal. Many physicians seem to have no faith in its value, but it should still be considered as important supplementary evidence. With its aid one may determine retention and stagnation, changes in acidity and the presence or absence of blood. The significance of all these findings has to be carefully weighed. Retention means obstruction of some kind and requires further investigation. If mechanical in character, cancer is a possibility especially if associated with absence of free hydrochloric acid, the presence of lactic acid and Boas-Oppler bacilli. On the other hand such findings are not pathognomonic of cancer. Normal acidity is not incompatible with the presence of a malignant growth. The presence of blood, likewise is merely an indication of an ulcerative lesion, but not necessarily

cancer. However, given a patient in the cancer age with characteristic symptoms and abnormal gastric findings, the probability of cancer must not be overlooked.

The most important diagnostic aid is a roentgen examination for evidence of a defect, rigidity of the wall, absence of peristalsis, and retention. The technique in experienced hands has developed to such a degree that a positive diagnosis can be made in the great majority of cases. There is no possible excuse for not having an x-ray examination of the stomach made in every patient with vague epigastric symptoms, except perhaps the cost involved. There is no doubt that many more examinations would be made were it not for the financial aspect of it. In the eyes of patients, expenditures like that are always justified with a positive finding, with a negative finding, however, a physician may be called an alarmist and the expense involved is charged against him. Even the affluent often hesitate at the cost of an x-ray examination unless symptoms are severe. Clinic patients of course have all the examinations made which are indicated. The people with small incomes in the great middle class find the cost of a gastrointestinal series beyond their resources. It is therefore frequently dispensed with, though indicated, in the hope that the symptoms may disappear. This point deserves stressing again and again.

If all attempts at diagnosis fail, and suspicion of malignancy persists, an exploratory operation should be considered. It should not be undertaken too lightly, but indications are that it might advantageously be resorted to more often than is the case.

Nothing very positive is known concerning the etiology. In most cases symptoms come on insidiously without any previous gastric disturbance. One is therefore compelled to admit that cancer is probably cancer right in the very beginning in the majority of cases and is not grafted upon a pre-existing disease. On the other hand, it may well develop in the changed mucosa of an old gastritis. The frequent finding of gastritis in connection with cancer lends credence to this theory. If we assume chronic irritation to be the starting point in other parts of the body, the stagnation and irritation due to pylorospasm in association with gastritis may well be an etiological factor. Another possibility is cancerous degeneration of an adenomatous polyp.

The question of the relationship of gastric ulcer and carcinoma is

very interesting and has aroused a great deal of discussion. Some clinics have reported a very high incidence, but the majority of conservative surgeons report between 10 and 20 per cent. There seems little doubt that a certain number of cancers develop on the basis of an old ulcer. In those cases in which ulcer symptoms long preceded the cancer, one may definitely have to assume this etiology. On the other hand the findings of an ulcer with carcinoma does not necessarily mean that the carcinoma has developed on an ulcer basis. Quite the contrary, a carcinoma may ulcerate and sometimes to such a degree as to destroy most of the cancer cells. The question has not yet been solved satisfactorily.

With the present state of our knowledge the treatment of cancer of the stomach is surgical. Experience so far has shown that x-ray treatment is helpful in alleviating symptoms in a small percentage of cases, but it is not curative. Surgery is strongly indicated and is life-saving in many early cases. Surgery is also indicated in more advanced cases, as a matter of fact an exploration should be done in all patients whose general condition warrants it. Though many will be found to be too far advanced, not infrequently one finds conditions more favorable than had been anticipated, and a resection may still be possible. In others a palliative procedure may be done, either a gastroenterostomy alone or combined with exclusion of the pyloric end containing the tumor.

A palpable tumor, even a large one, is no contraindication to operation, it may be found to be readily removable. Any tumor which is removable, is operable. One should not be frightened by the presence of enlarged lymph nodes, but remove them with the specimen. Enlarged lymph nodes do not necessarily mean involvement. They may be inflammatory in character due to absorption from an ulcerating carcinoma.

In a planned operation for cancer of the stomach which is not an emergency, ample time is available to prepare the patient properly for the procedure. This is one of the most important steps in the handling of the patient, and in connection with improved surgical technique is responsible for the lowered mortality at the present time. Under pre-operative treatment may be mentioned attention to the heart, kidneys and lungs in order to build up the patient's resistance. The most important steps, however are the administration of sufficient quantities of fluids by venoclysis or hypodermoclysis to overcome dehydration and toxemia, daily gastric lavage to remove stagnated contents, overcome edema and prevent absorption, oral administration of nutritious fluids which may

still pass through the pylorus, and transfusions to raise the lowered vitality

Thus prepared, the patient is a far better risk and the surgeon may perform a radical operation which otherwise would seem too hazardous. The operability for cancer of the stomach has been definitely extended by the application of effective preoperative care, so that from 40 to 45 per cent are now operable whereas some years ago, operation was advisable in less than 25 per cent.

The ideal operation consists of the removal of the tumor with a safe margin of normal tissue above and below the lesion and the removal also of the regional lymph nodes along the lesser and greater curvature. Just which technical procedure is used is a matter of the personal preference of each surgeon. The Billroth II method is the one most frequently employed in cancer because of certain advantages over others. Inasmuch as both ends, the duodenum as well as the proximal stomach, are permanently closed, one may make use of the von Petz sewing machine, which is time saving and effectively closes off the ends of the specimen and thereby prevents soiling. It has the further advantage that the gastroenterostomy is placed higher up on the stomach stump which would more certainly provide an open stoma even if a local recurrence should develop.

The postoperative mortality is influenced by many factors. It is no doubt higher with a high operability because if a surgeon takes a chance to extend the benefits of a radical resection to those who would be rejected by others, some increase in mortality rate may be looked for. However in the hands of good surgeons the increased risk may be compensated for by the greater skill. About 20 per cent is perhaps as low as may be expected with a high degree of operability.

The final results are the index of the value of radical operation. Considering untreated carcinoma of the stomach a rapidly fatal disease, it is gratifying to know that with an operability of 40 to 45 per cent a five year result of 30 per cent or more may be looked for. The following table published by Balfour is an indication of the progress which has been made.

Our own results, though covering only a small series of cases, correspond rather closely to those of Balfour. We have extended operability to include very difficult cases which would probably have been rejected by many surgeons for a radical procedure. From the results one may gain some encouragement in continuing the fight. Improvement is to be looked



TABLE I

*Operative Experience in Carcinomata of the Stomach (Balfour)*

<i>Procedure</i>	<i>Number of Cases</i>	<i>Percentage</i>
Resections	2,112	45%
Gastroenterostomy	815	17%
Exploration	1,866	38%
Total	4,793	100%
Five Year Results		
With lymph node involvement		18%
Without lymph node involvement		48%

TABLE II

*Operative Experience in Carcinomata of the Stomach (Faggers)*

	<i>Number</i>	<i>Percentage</i>
Total Number of Cases	63	100 %
Resections	28	44 1%
Postoperative mortality	5	17 9%
<hr/>		
Total resections of five years' standing	18	
Lymph node involvement present in	12	
Survivors in five-year-resection series	6	
Five-year survivors in which lymph node involvement was present	1	

for in earlier diagnosis, proper preoperative care of the patient, and good surgery

## CANCER OF THE COLON

Under this heading are presented malignancies of the cecum, ascending, transverse and descending colon, as well as those of the sigmoid. The reason they are classed in a group by themselves, in distinction from those of the rectum and rectosigmoid, is that there is a marked difference in the therapeutic problems involved. In the former group it is usually possible after resection of the affected portion to reestablish continuity of the gut with subsequent normal bowel function. In the latter group on the other hand a permanent artificial anus is the usual price the patient has to pay for a cure or attempted cure.

Cancer is much more common on the left than on the right side of the colon, the proportion being about two to one. The most common site is the sigmoid. It is well known that cancer has a tendency to develop where anatomically the gut is the narrowest. Surgeons and pathologists have speculated on the underlying reasons for this and it seems probable that the difference in the lumen with the added opportunity for stagnation and irritation play a rôle. Added to this one may consider

that the more solid constituents of the colon on the left side and the great accumulation of toxic products are factors. Of late years the frequent occurrence of polyp of the sigmoid and rectum with malignant degeneration has attracted considerable attention. Experience has further shown that usually tumors of the right side of the colon are less dangerous than those of the left, with respect to infection, as well as to the tendency to metastatic invasion of lymph nodes and the liver. It is interesting to observe that pathologically there is frequently quite a difference in the type of tumor encountered. On the right side they are usually flat, or ulcer like, or large bulky masses, while sigmoid tumors are frequently small scirrhus growths which encircle the gut.

These various considerations to a large degree explain the difference in symptomatology, and provide a reasonable explanation for the fact that most patients come under observation only many months after the first manifestation of symptoms. A tumor developing in the large cecum for instance, does not interfere with bowel function, it does not bleed until it ulcerates and it may not produce a palpable tumor. It therefore escapes attention until a massive tumor either becomes palpable and begins to obstruct the flow of intestinal contents, or by ulceration and absorption of breaking down tumor tissue, produces toxemia, bleeding and anemia. A similar tumor at a narrow portion of gut, such as the hepatic or splenic flexure may produce narrowing of the lumen early and thereby lead to recognition. In the sigmoid on the other hand, an encircling scirrhus tumor which grows slowly, may not lead to striking symptoms until actual obstruction suddenly appears. The symptomatology depends chiefly on the interference with the flow of intestinal contents. Obstruction at some time in the course of the disease is the chief symptom. It is usually chronic, but not infrequently acute obstruction supervenes, especially in the sigmoid. In any middle aged or elderly person with obstruction, if strangulated hernia or bands of adhesions can be ruled out, carcinoma of the colon is the most rational diagnosis.

The obstruction is usually slow and progressive which permits the gut to accommodate itself to the changed condition by hypertrophy of the bowel wall and by rendering fluid the intestinal contents above the obstruction in order to permit passage through the narrowed portion. The resulting changes in bowel habit, consisting of either increasing constipation, or attacks of diarrhea, or alternation of these symptoms, may early draw attention to the real underlying cause. If a temporary

acute obstruction supervenes which so frequently happens when a hard particle of feces or a foreign body becomes lodged in the stenosed gut, investigation is urgently called for. While these changes gradually take place in the gut, the general health suffers due to dehydration and toxemia, and a progressive loss of weight and strength results. At times there is marked anemia especially with the large bulky tumors. Ulceration usually takes place in the tumor with consequent toxic absorption and bleeding. Examination of the feces therefore frequently results in the finding of blood. It may be occult if coming from a lesion higher up in the colon, or bright red, accompanying defecation or clinging to the fecal masses, if arising from a tumor situated in the lower colon.

Patients not infrequently complain of pain, usually cramp-like in character and associated with the retention of gas. They often feel gas "stick" in a certain place and possibly always in the same place, which is a symptom requiring investigation. They may feel and hear gurgling in the intestines and have general discomfort. At times they have explosive movements. All of these symptoms are important if appearing in a patient who has formerly not suffered in this way, and they call for investigation. On examination one may find nothing abnormal, especially not if the abdomen is distended. Many elderly people habitually have a distended abdomen and in that case it is of no value as a diagnostic sign. However, if it has appeared but recently this distention in itself may be an important sign. One may be able to elicit tenderness, particularly over a distended loop proximal to a growth, and one may be fortunate enough to detect peristalsis. This, however, is usually present only in an advanced case with threatening obstruction. At times a tumor mass is palpable. The examiner may discover this accidentally during a routine manual examination or his attention may be drawn to it by local symptoms. Tumors of the cecum, sigmoid and other parts of the colon may thus be palpated but those of the hepatic and splenic flexures are frequently hidden.

Most important in the diagnosis is an x-ray. Experience has shown that a barium meal when it hardens in the intestines is liable to block a stenosed lumen of gut and thereby precipitate an acute obstruction. Physicians have therefore largely abandoned this method of examination as a routine in all suspected malignancies of the colon, and are resorting to a barium clysis instead. It is safer, the findings are known more promptly and the results of examination are generally more satis-

factory With proper preparation of the colon in a suspected case the demonstration of a defect in the lumen is usually not difficult However, overlapping of a tumor by a loop of gut filled with barium has frequently led to errors in diagnosis, especially so with a redundant sigmoid In order to avoid such errors roentgenologists have developed a special technique for colon lesions A prerequisite is a clean colon, best obtained with the aid of an enema or irrigation The contrast mixture is then allowed to run in slowly under guidance of the fluoroscopic screen Abnormalities are noted and plates are then made in different positions One of the most important is the oblique which permits unfolding of the entire sigmoid with the aid of a certain amount of pressure After defecation additional plates should be made Lately a special technique which makes a study of the mucosal pattern possible, has been added to the diagnostic resources of the roentgenologist In cases of acute obstruction also, the x-ray has a certain value An ordinary flat plate may show distended loops of gut containing air, or there may be fluid levels in the lumen A carefully administered barium clyisma may show the site of obstruction and thereby aid in the selection of the indicated operative procedure

The treatment depends on the location of the lesion, as well as on the state of the disease In acute obstruction one has different problems to consider than in chronic incomplete obstruction or in early cases The immediate indication in acute conditions is relief of the obstruction, usually by means of a cecostomy or a colostomy A preliminary x-ray may help in choosing the proper site for the incision The question of coping with the tumor comes up for consideration after the acute symptoms have subsided

In all early cases and in those with chronic incomplete obstruction a planned operative procedure is possible This should be preceded by a period of preparation to allow local inflammatory conditions to subside and to build up the general resistance of the patient Especially if there have been attacks of obstruction the gut wall is edematous and infiltrated and there may be a certain amount of pericolic inflammation Daily enemas or laxatives, combined with bed rest, will help to restore tissues to a condition which permits handling with less danger of spreading infection If it cannot be accomplished in this way a preliminary cecostomy or colostomy is indicated In the meantime measures are undertaken to increase the patient's general resistance This is done by

the administration of nutritious fluids by mouth, or by venoclysis and hypodermoclysis. Transfusions are of great value and should be resorted to freely.

The operative procedure itself varies with the location of the tumor. In lesions affecting the ileocecal junction, the cecum, ascending colon and hepatic flexure, a resection of the right side of the colon with subsequent ileocolostomy is the operation of choice. In suitable cases the entire procedure may be carried out in one stage. In case the patient's general condition is not favorable, or if there have been obstructive signs, it is best to divide the operation into two stages. The first step consists of doing an ileocolostomy by uniting the distal end of the ileum with the transverse colon. It usually results in prompt improvement in the patient's condition which will permit the second stage to be performed after a few weeks. The abdomen is opened through the same incision and the entire right colon with the stump of the ileum and all lymph nodes, removed in one mass.

Tumors of the transverse colon, the splenic flexure or the descending colon are best handled by resection and subsequent end to end or lateral anastomosis. It may be done in one or two stages as indicated. A certain amount of mobilization of the gut is usually required to permit suture without tension.

The most important tumors of the colon, from the standpoint of frequency, therapeutic problems involved, and danger, are those of the sigmoid. Unfortunately a large percentage of patients with carcinoma of the sigmoid are admitted with symptoms of acute obstruction, while others are so far advanced that complete removal is not possible. The most ideal are naturally those without lymph node involvement. Prognosis in those patients is very good, though sometimes there are early metastases to the liver.

The Mickulicz operation is commonly employed. It is efficient when no nodes are involved and the sigmoid is long and has a wide mobile mesentery, so that one may simply bring out a loop of gut with the tumor without interfering with its blood supply. However, if the tumor is large and fixed, the mesentery short and lymph nodes involved, the operation has serious shortcomings. If one attempts to get beyond the nodes at the first stage, one may interfere with the blood supply and cause gangrene beyond the exteriorized loop, resulting in leakage and peritonitis. It has the additional disadvantage in such cases of making it

practically impossible at the second stage to get beyond the nodes because of matting together of the tissues. One, therefore, may have to be satisfied with an incomplete operation. For these reasons different methods of procedure have been advised. One may at times perform a primary resection, and in our hands this has given very good results in properly selected cases. In other cases one may effect either a cecostomy or a colostomy proximal to the tumor for decompression of the bowel, and later follow with a resection of the tumor and anastomosis of the gut. Rankin is a strong advocate of what he calls obstructive resection of the gut, after preliminary decompression.

Whatever method one chooses, it is important to resect the tumor together with the lymph nodes draining the affected portion of gut. It is a safe procedure after edema and infection have been overcome by draining and irrigating the bowel. Rankin with his extensive experience has some very illuminating statistics concerning five year results. He further demonstrates that the intrinsic activity of the cancer cell as measured by Broder's classification of malignancy plays an important rôle in these results. He points out that most cancers of the colon fall into the lower grades where metastases are slower, lymph node and hepatic involvement correspondingly lower, and in consequence, the result more favorable following successful removal.

TABLE III

*Operative Results in Cancer of the Left Colon (Rankin)*

	Grade 1	Grade 2	Grade 3	Grade 4
Incidence	13%	67%	16%	4%
Five year cures	63%	51%	30%	18%

Our own experience with carcinoma of the sigmoid prior to five years ago is limited to twenty-one cases.

Five patients, or 31.2 per cent, are living over five years, as follows: thirteen, ten, nine, eight and six years. Two of these five, or 40 per cent, had lymph node involvement.

TABLE IV

*Operative Experience with Carcinoma of the Sigmoid (Eggers)*

	Number	Percentage
Total cases	21	
Inoperable	5	23.7%
Operable	16	76.3%
Five year survivors	5*	31.2%

\* Two of these five, or 40 per cent, had lymph node involvement.

## CANCER OF THE RECTUM AND RECTOSIGMOID

Cancer of this region presents diagnostic and therapeutic problems quite different from those of the colon. While the lesions originating in the rectum may reach a considerable size before symptoms manifest themselves, those beginning higher up, at the rectosigmoid junction, may give rise to obstruction early. Blood in the stool or clinging to the outside of the stool is a common finding, and should insure a most careful examination with the finger and proctoscope. Too often such bleeding is attributed to the presence of hemorrhoids, and not infrequently operation for this condition has been undertaken only to find later that a carcinoma was the underlying cause. Associated with blood in the stool there may be a feeling of discomfort and pressure, as well as a change in the bowel habit, consisting of increasing constipation, perhaps alternating with diarrhea. At times the patients mention explosive movements of gas and thin feces which are due to the collection of fluid intestinal contents above the obstruction until the pressure reaches such a point that they are forced through. Tenesmus and pain may be present, but are often an indication of a more advanced lesion which has become fixed and exerts pressure. Blood in the stool, associated with change in the bowel habit, and fullness or pressure in the rectum should always call for careful investigation. A digital examination must never be neglected, and reveals the size and exact position of any tumor situated in the lower colon. Even the higher lesions can usually be palpated. One may have the patient return for a re-examination after the bowels have been prepared with a cleansing enema. With the patient lying on the side, or in the knee chest position, or in a squatting position, the examining finger can usually reach the growth when the patient is told to bear down. A biopsy may at times be performed without difficulty, but if the tumor is not readily accessible, it should be deferred until after admission to a hospital. In case the suspected growth is not palpable a proctoscopic examination should be done and will usually show a growth within that portion of gut under consideration. Should the examination be negative a barium clysma is indicated, using the technique described under sigmoid lesions.

Theoretically considered carcinoma of the lower segments of the bowel should be diagnosed early because of their symptoms and easy accessibility. Unfortunately that is not the case. For those tumors sit-

uated at the rectosigmoid junction an alibi may sometimes be advanced, in that the tumor has an unfortunate location for diagnosis. It is just too low to be palpable from above and too high to be felt from below. The x-ray may be negative because of an overlapping loop. The employment of oblique x-rays and the more frequent use of the proctoscope should overcome these difficulties. For failure to diagnose tumors situated low, no alibi exists.

In contemplating treatment one has to consider what one wants to accomplish, namely extirpation of the growth together with the lymph nodes draining that area. This latter is essential because almost half of the patients have lymph node involvement at the time they come under observation. To do a palliative operation would be to exclude all these from any consideration of attempted cure. Radium is advocated by some radiologists for tumors situated low, and good results are claimed. Nevertheless the curative value of radium is not well established and is limited to the primary tumor. Electrocoagulation which has recently been mentioned as a method of treatment probably also has a limited usefulness in readily accessible tumors. Great care is required to prevent perforation into an organ or into the peritoneum. Good results have been reported and it may be well to keep it in mind as a method of treatment in selected cases. The greatest objection to it as an attempt at cure is the fact that the lymph nodes are not removed. It would therefore seem to have its greatest field of usefulness in tumors which have remained localized, and as a palliative measure.

Radical operative removal offers the best chance for cure. Several methods of approach and their modifications are available. Surgeons differ somewhat concerning the best method of procedure, whether to attack by the perineal route with or without a preliminary colostomy, or to perform a radical abdominoperineal resection in one or two stages. Less extensive procedures, such as local excision or resection of the rectum with preservation of the sphincter, find application only rarely in well selected cases. There is no doubt that in tumors situated low, a perineal operation may be carried out with sufficient mobilization of the gut to permit resection of the tumor bearing area and suture of the stump to the skin, leaving the new anus in its normal position, without the necessity of a colostomy. There is of course no sphincteric action, but a certain amount of control develops eventually with the aid of the levator muscles and contraction of the opening. Even growths situated



higher may be safely removed from below after a preliminary colostomy which remains permanently. From the standpoint of cancer surgery, however, which aims to remove the primary tumor together with the lymphatic drainage area, there is no question that the abdominoperineal operation is the preferable one. It is readily understandable, therefore, that at the present time surgeons generally are leaning towards the latter procedure.

One of the most important steps in the successful treatment of cancer of the rectum and rectosigmoid is preoperative care consisting of decompression of the bowel, administration of fluids, transfusion, attention to the heart and kidneys. Operation should be delayed until the patient has been rehabilitated, especially if obstructive symptoms have been present. In such a case division of the abdominoperineal operation into two stages, the first one consisting of a colostomy, is advisable.

With proper preoperative care the operability may be extended, operative mortality reduced and good permanent results obtained. In order to judge reported results one has to know the percentage of operability, as it is easy to have a high percentage of five year results with carefully selected cases.

TABLE X

*Carcinoma of Rectum and Rectosigmoid (Tager)*

Total Cases	24
Inoperable	8 or 33.3%
Operable	16 or 66.6%
Mortality	2 or 12.5%
Five Year survivors	5 or 31.2%
Still Living (Six, seven, ten and thirteen years)	4 or 25%

With an operability of 66.6 per cent and a mortality of 12.5 per cent, we have survivors of five years, and longer, of 31.2 per cent.

Rankin, with an operability of 76 per cent has 34 per cent five year survivors.

TABLE XI

*Carcinoma of Rectum and Rectosigmoid (Rankin)*

Total Cases	300
Operability	76%
Five Year Survivors	34%

Rankin reports Miles with an operability of 30 per cent and 79 per cent five year survivors, while Jones with a higher operability had 50 per cent five year cures.

Such results can be obtained only in carefully selected cases. With the types of patients presenting themselves to us we feel that we cannot refuse to operate upon all but 30 per cent, and our operability has therefore been extended to include more than twice that number. To obtain good results in such cases should be our aim, and we feel that it is possible by proper preoperative care, and selection of that type of operation which the patient is able to stand and which gives greatest promise of restoration to health. We believe that in tumors situated at a high level, an abdominoperineal operation, performed in one or two stages, has definite advantages because it offers better control of the blood supply, and is therefore less shocking than a perineal operation. In addition to that it gives greater assurance of going well beyond the growth as well as including the involved lymph nodes.

The problems in treatment are well understood and have been largely mastered. The greatest need at present is early diagnosis. The thoughts we would like to leave with you are that cancer in its early stages is curable, cancer in a more advanced stage may still be curable, and that every patient with a positive diagnosis of carcinoma of the gastrointestinal tract is entitled to an exploratory operation, if his general condition permits.

## CLINICAL ASPECTS OF HYPERTENSION INCLUDING MALIGNANT HYPERTENSION

HERMAN O MOSENTHAL

Professor of Clinical Medicine New York Post Graduate Medical School Columbia University

### NORMAL BLOOD PRESSURE

**A**N exposition of the clinical aspects of hypertension must have as its starting point a conception of normal blood pressure. Normal blood pressure may be defined as the arterial blood pressure which is sufficient to cause the blood to flow and to deliver a pressure of thirty to forty millimeters of mercury (the pressure necessary to accomplish metabolic exchange) in the proximal part of the capillaries. When the heart and the arteries are intact, and not affected by the degenerative processes of aging, this arterial pressure is about 100 systolic and seventy diastolic, the accepted normal pressure for a child of ten (Judson and Nicholson,<sup>1</sup> Hunter<sup>2</sup>). Any blood pressure above this level is hypertension. The persistence of a youthful blood pressure in adult life is indicative of an absence of arteriosclerotic processes and is not necessarily a hypotensive state as is so often assumed.

### AVERAGE NORMAL BLOOD PRESSURE

Advancing years are, as a rule, accompanied by an elevation of blood pressure. The systolic pressure increases more than the diastolic and, consequently, the pulse pressure rises. According to Hunter's well-known table, between the tenth and sixtieth year, the systolic pressure increases thirty-two millimeters of mercury, the diastolic nineteen, and the pulse pressure thirteen. The routine explanation offered for these changes is that through arteriosclerotic processes, natural with aging, the arteries lose their elasticity and become more rigid. These qualities may be measured according to pulse velocities which are found to increase considerably in both the elastic and the muscular arteries (Hallock<sup>3</sup>—Chart 1).

A rigidity of the arterial wall due solely to arteriosclerosis would result in a rise of the systolic pressure, but not of the diastolic, the latter

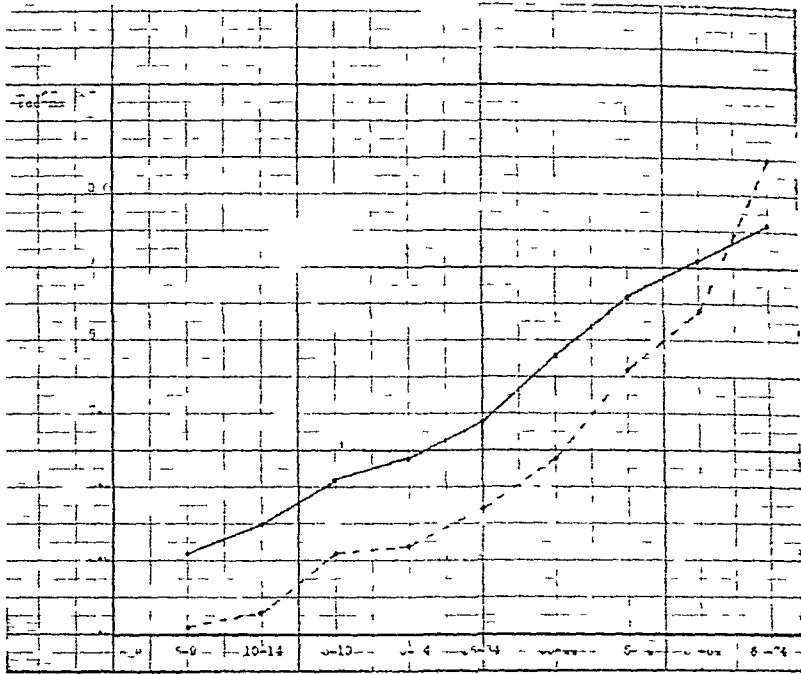


CHART I

*Wave Velocities in Elastic and Muscular Arteries at Various Ages*

Mean wave velocities (meters per second) in the aorta (elastic artery) and radial artery (muscular artery) at various ages, according to Hallock, *Arch Int Med* 1934, 54: 770. Both aortic and radial velocity increase with age. After 55, aortic velocity increases more rapidly than radial; these facts point to a difference between the processes producing rigidity (or loss of elasticity) in the elastic and muscular arteries (arteriosclerosis of elastic and muscular arteries and the degree of muscular tone in the muscular arteries must be considered).

should under such circumstances diminish rather than increase. The fact that the diastolic pressure goes up shows that another element in blood pressure production besides the purely mechanical development of arterial rigidity is involved. It is suggested that the rise in diastolic pressure in the older age periods is due to an augmented tonicity of the muscular arteries. Such a compensatory elevation of tone in the musculature of the larger arteries appears to be the only explanation for the rise in diastolic pressure; it would also account for the increase of pulse velocity in the muscular arteries. A controlled diminution of elasticity of this sort would give the clue to the reason for the almost exact parallelism between the rising pulse velocity and diminution of arterial elasticity with age in the elastic and in the muscular arteries (Chart 1).

### MARKED SENILE ARTERIOSCLEROSIS AND BLOOD PRESSURE

The steady progress of arteriosclerosis in the elastic arteries has been mentioned in the previous section. At sixty years, according to Aschoff,<sup>4</sup> the aorta is practically devoid of elasticity. Decrescent changes in the muscular arteries are characterized by calcification of the media—the type of arterial involvement known as Moenkeberg's sclerosis. In many instances although the calcinosis of the blood vessels may be palpated and demonstrated by x-ray, there are no corresponding changes in the blood pressure. This has been attributed by Haynes, Ellis and Weiss<sup>5</sup> to the patchy occurrence of medial calcification—certain areas of the arterial wall being left intact to control the blood pressure. When the entire arterial system becomes sclerotic and rigid it is believed that the systolic pressure becomes very high, the diastolic very low, and the pulse pressure correspondingly large (Bowes,<sup>6</sup> Thompson and Todd<sup>7</sup>).

### INCREASED SYSTOLIC OUTPUT AND BLOOD PRESSURE

A rise in pulse volume results in an elevated systolic and a comparatively low diastolic pressure. This occurs with a slow heart rate, especially in heart block, with hyperthyroidism (Read<sup>8</sup>) and with aortic insufficiency. In heart block (Ellis and Weiss,<sup>9</sup> Ellis<sup>10</sup>) and in hyperthyroidism various factors may compensate for the tendency to hypertension and the blood pressure may be normal in spite of an increased systolic output. The spread between the systolic and diastolic pressure in aortic insufficiency depends largely upon the degree of valve leakage. The pulse pressure may be very high, but in some cases it is approximately normal. Aortic insufficiency should be suspected whenever the pulse pressure is as great as sixty millimeters of mercury.

### HIGH SYSTOLIC, LOW DIASTOLIC PRESSURE OF MIDDLE AGE

This type of blood pressure is often found, especially in women after the menopause (Saller,<sup>11</sup> Riesman<sup>12</sup>). Calcinosis of the muscular arteries is absent and, consequently, the comparatively low diastolic pressure can not be explained upon the basis of diffuse rigidity throughout the arterial tree. It may be that in such cases there is a lack of compensatory rise in tonicity of the muscular arteries which has been cited in explanation of the elevation of the diastolic pressure in the average normal blood pressure. The frequent occurrence of high systolic pressure and low diastolic pressure, without demonstrable pathological lesions of any sort, should be

recognized The prognosis of this type of hypertensive disease is much better than when the diastolic pressure is also elevated, and a sharp distinction should be made in the treatment accorded these two varieties of hypertension

### DIET AND BLOOD PRESSURE

*Proteins* The contention that protein foods do not bring about a rise in blood pressure (Mosenthal<sup>13</sup>) has proved to be correct There is one exception to this statement which may or may not be of clinical significance Chanutin and Ludewig<sup>14</sup> found that all rats from whom eighty to ninety per cent of the total renal tissue had been removed (corresponding to uremia or a preuremic condition in man) showed hypertension, and that the degree of blood pressure elevation was directly proportional to the amount of protein fed On the other hand I have found that in human beings with renal insufficiency the blood pressure remains unchanged when the blood urea and the non-protein nitrogen rise or fall markedly in response to dietary regulation

*Carbohydrates and fats* There is no reason to believe that carbohydrates or fats have any influence upon blood pressure except in so far as they may cause obesity Overweight, contrary to former impressions, does not result in hypertension, but it should be avoided because it places an additional strain upon the heart and arteries A high blood sugar, whether of short duration or persistent, does not give rise to hypertension (Mosenthal<sup>15</sup>)

*Fluids* Since transfusions of as much as 1000 cc, even when given rapidly, do not affect the blood pressure (Mosenthal and Ashe<sup>16</sup>), it is not surprising that the ingestion of large amounts of fluid do not raise the blood pressure (Orr and Innes<sup>17</sup>) The fluid intake should be restricted in the presence of cardiac weakness or edema

*Alcohol* In moderation, alcohol does not influence blood pressure, the hypertension of habitual, heavy drinkers is, in some instances, lowered when the alcohol is restricted or total abstinence is practiced

### BLOOD VOLUME AND BLOOD PRESSURE

One of the assumed causes for hypertension has been, and is, a large blood volume I remember Theodore Janeway's disappointment when Keith, Rowntree and Geraghty<sup>18</sup> failed to demonstrate an increased blood volume in hypertensive cases This finding does not eliminate

an augmentation of the blood mass as being a possible factor in elevating arterial pressure. Polycythemia vera is usually cited as a condition in which this occurs, though in this disease the increased blood viscosity must also be considered (Brown and Griffin<sup>19</sup>).

The blood pressure, even when marked hypertension exists, does not rise, but remains unchanged under the stress of rapid transfusions of 1000 cc of blood (Mosenthal and Ashe<sup>16</sup>). This shows that the body possesses excellent powers of regulating the arterial pressure in the face of enormous variations in blood volume.

The key to the situation probably lies in the fact that the arterial, pulmonary, capillary and venous regions have different functions in regard to the storage of blood. In the capillaries and veins a rise in blood volume should be harbored without difficulty while the quantity of blood remains constant in the arterial system.

Data published by Plesch<sup>20</sup> show that the arteries of the greater circulation contain approximately 250 cc of blood (Table I), that is, about the full capacity of the ordinary water tumbler. This is very surprising to most of us but it seems plausible when the matter is analyzed according to the table.

TABLE I

Distribution of blood in the circulation according to Plesch. Note the small volume in the arteries and the large volume in the capillaries and veins, indicating the possibility of their accommodating large fluctuations in the blood mass without disturbing blood pressure or the circulatory flow.

		Blood Volume cc	
SYSTEMIC CIRCULATION	Arteries	250	} 2500
	Capillaries	1310	
	Veins	750	
	Left Heart	190	
PULMONARY CIRCULATION	Arteries	125	} 2000
	Capillaries	1310	
	Veins	375	
	Right Heart	190	
	TOTAL		4500

When we realize that the quantity of blood contained in the arterial system, that is, between the aortic valves and the arterioles, can be measured in a tumbler, and is only a small fraction of the gallon or more which constitutes the total blood volume, it becomes easier to understand the great effect upon arterial pressure of what at first thought appear to be comparatively small changes in systolic output, arterial elasticity,

the tone of the muscular arteries and the contraction or dilatation of the arterioles. The maintenance of a more or less constant blood pressure while the heart and arteries are anatomically and functionally intact, and the extreme lability of blood pressure when the compensatory mechanism is impaired, become less of a mystery when we consider that the arterial blood volume is only a small part of the total blood volume.

### HYPERTENSIVE DISEASE

All the varieties of hypertension mentioned thus far are characterized by an absence of rise, or a comparatively slight rise of the diastolic pressure. Hypertension, when it becomes a threat, through the strain it imposes upon the heart and the blood vessels, exhibits not only an elevation of the systolic but also a distinct increase in the diastolic pressure. An hypertensive state is considered severe when the diastolic pressure reaches a level of 130, 140 is of common occurrence, values as high as 200, or more, sometimes develop.

True hypertensive states, that is those in which both systolic and diastolic pressures are very much elevated, present themselves in three forms to the clinicians:

- 1 Hypertension accompanying albuminuria
- 2 Hypertension as a sequel to renal dysfunction
- 3 Idiopathic (essential) hypertension

*Hypertension as an accompaniment of albuminuria* was first recognized by Bright<sup>21</sup> in 1836, when in his series of "Cases of renal disease accompanied with the secretion of albuminous urine", he observed thirty-four cases of cardiac hypertrophy without any valvular disease. The hypertension associated with acute nephritis is well known, it is usually of short duration and is outside the present topic. Herrick and Tillman<sup>22</sup> found that a small but appreciable number of toxemias of pregnancy, when followed up, developed hypertensive disease after an initial albuminuric nephritis. The observation over a number of years of cases which began as albuminuria, in men as well as in women, has led me to the conclusion that hypertension frequently becomes the dominant complication of albuminuria and outstrips renal insufficiency, anemia or uremia as a cause of death. It may be that with the recent advances in the treatment of albuminuria, these patients live long enough to develop hypertension instead of succumbing to infections, as was so common a decade ago.



*Hypertension as a sequel to renal dysfunction* may be discussed under the headings

- 1 Influence of hypertension on renal function
- 2 Influence of diminished renal function on blood pressure
- 3 Influence of renal ischemia on blood pressure

The theory that hypertension was a compensatory process to enhance the action of the kidneys was first formulated by Traube<sup>23</sup> in 1876 and subsequently endorsed by Cohnheim<sup>24</sup> in 1880. Recently, in 1934, Page<sup>25</sup> showed that neither a spontaneous nor an induced fall of blood pressure affected renal function as measured by the urea clearance test. This evidence which bears out many clinical observations, sets aside the compensatory theory of the cause of hypertension. The level to which the blood pressure may be depressed without interfering with kidney activity of course has its limits. Lassen and Husfeldt<sup>26</sup> found when the systolic blood pressure had been lowered to well below 100 by means of spinal anesthesia, that the urinary flow was diminished. Such degrees of hypotension (the diastolic pressure presumably being fifty mm of mercury or less) fail to deliver a glomerular capillary pressure of thirty or more to overcome the plasma colloid osmotic pressure of about thirty, a pressure which Richards<sup>27</sup> and his co-workers have found necessary for urine formation.

The demonstration that destruction or removal of the greater part of the kidneys is followed by an elevation of blood pressure, was first accomplished by Passler and Heineke<sup>28</sup> in 1905. Janeway<sup>29</sup> in 1913 showed that after reduction of the dog's kidney substance there was a rise not only of the systolic pressure, but of the diastolic as well. Subsequent experimental work has amply verified these observations.

The clinician knows that hypertension follows renal insufficiency, whatever its cause. This holds true whether deficient kidney activity is due to obstruction of the urinary tract, Bright's disease or other renal involvement, such as polycystic degeneration of the kidneys. The proof of the causal relationship between hypertension and impaired kidney function is found in the fact that when obstruction of the urinary tract (whether it is due to new growth, stricture, stone or prostatic hypertrophy) is relieved, the blood pressure returns to a normal level. Frequently, hypertension does not develop with inadequate renal function, or drops while kidney activity is still diminished. The lack or blood pressure elevation under such circumstances is attributed to con-

stitutional weakness which lessens the power of the cardiac and arterial muscles

Ischemia of the kidney, produced experimentally by constriction of the renal artery, results in a rise of blood pressure. This is a noteworthy contribution by Goldblatt,<sup>30</sup> its exact clinical application is not yet clear though without doubt it will prove to be important.

*Essential—idiopathic—Hypertension* Essential hypertension may be defined as a functional disorder, characterized by a *progressively increasing* elevation of *both systolic and diastolic* arterial pressure, the mechanical strain incidental to the hypertension often produces changes in the heart and the arteries, especially those of the heart, the brain and the kidneys, so severe that death results.

Recognition of the independence of blood pressure from kidney disease in a certain group of cases, dates from a period after the invention of the first clinical instrument for measuring blood pressure by von Basch in 1876, and was formulated in terms that explained the trend of thought at that time.

“Latent arteriosclerosis”—von Basch

“Pre-sclerosis”

“Pre-albuminuric stage of Bright’s disease”—Mahomed

“Hyperpiesis”—Clifford Allbutt

“Hypertensive cardiovascular disease”—Janeway

“Essential hypertension”

“Malignant hypertension”—Keith, Wagener and Kernohan

All these terms indicate that various clinicians have demonstrated to their satisfaction for many years that high blood pressure may occur independently of any affection of the kidneys. This is not recognized in all quarters today. Such doubt of the frequent independence of hypertension and kidney disease still rests very largely on the impressions of clinicians and pathologists antedating the perfection of renal function tests.

Any one who has studied cases of elevated arterial pressure during the last twenty years, knows that the patients with hypertension and without demonstrable lesions of the kidney or impairment of renal function, are numerous. A careful analysis of mortality statistics shows that the majority of deaths of persons between forty and sixty-five years of age, that is, individuals who die before they have lived their natural life span, is due to the sequelae of hypertensive disease.

The capillary pressure remains normal in hypertensive subjects, showing that the peripheral resistance is adjusted so that a normal capillary circulation is maintained. This was first demonstrated by Boas and Frant<sup>31</sup> in 1922 and since then has been verified many times. The question arises whether the peripheral resistance is primary and the hypertension a compensatory phenomenon, or whether the hypertension in the arteries initiates the vicious circle and is regulated by the arterioles at the distal end of the arterial tree.

The generally accepted view is that a generalized contraction of the arterioles causes hypertension. The idea that increased tonicity of the muscular arteries may bring about an elevation of the blood pressure and that the arterioles act as regulators which control the flow of blood to the capillaries, has been ignored and never refuted though it has been stressed by Pal<sup>32</sup> and others.

There is a good deal of evidence that the arterioles contract and dilate according to the local requirements of the tissues which they supply with blood. The observations of Krogh,<sup>33</sup> Richards,<sup>27</sup> and Cobb and Talbott<sup>34</sup> have shown that during quiescence only a fraction (in the kidneys 5 per cent) of the capillaries are patent in the voluntary muscles, kidneys, brain and presumably all tissues, while during periods of activity, all the available capillaries are open and filled with blood. It seems rather forced in view of these facts, to think of a generalized, fixed, peripheral resistance as existing throughout the body, since it is clear that the intermittent blood supply is adjusted by constant openings, contractions and closures of the arterioles which do not occur simultaneously throughout the whole body but are brought into play according to the needs of the individual tissues.

Two recent observations establish the fact that arterioles dilate or contract in response to a drop or increase in blood pressure. Page and Heuer<sup>35</sup> found that after section of dorsal and lumbar anterior nerve roots a drop in arterial pressure was accompanied by relaxation of spasm in the arterioles of the retinae though they were outside of the operative field, that could influence the retinal vessels directly. Flexner<sup>36</sup> studied the peripheral circulation in a case of coarctation of the aorta and demonstrated that the action of the arterioles was about the same in the arms where hypertension had resulted from aortic narrowing, as in the legs where the blood pressure was at a normal level.

All these points are arguments for the idea that increased arteriolar

or peripheral resistance is a compensatory phenomenon for a hypertension produced by other agencies presumably an augmented tonicity of the muscular arteries

### MALIGNANT HYPERTENSION

Volhard and Fahr<sup>37</sup> in 1914 coined the term "malignant hypertension" for those cases in which a high blood pressure was complicated by renal insufficiency. The name was abandoned until Keith, Wiggner and Kernohan revived it and stressed neuroretinitis and hypertensive encephalopathy as the significant complications. Since then malignant hypertension has been defined in a great variety of ways, very few of which accord with one another. The malignant nephrosclerosis, first described by Fahr,<sup>38</sup> has been recognized and this designation has a justifiable background. Instead of thinking of essential hypertension as benign or malignant, it would serve a better purpose to classify this condition as mild or severe, the severe type including the cases with a diastolic pressure constantly above 140 or more, which constitutes a menace through various vascular complications. It is true that such hypertensive states often "manifest extreme malevolence" and in that sense are malignant but in clinical parlance the term malignant hypertension is associated with the complications of hypertension which, according to some, are not necessarily present, according to others, may be either retinal or renal or cerebral. There is no unanimity as to the exact symptom complex covered by the term malignant hypertension, and it would serve accuracy and simplicity if it were abandoned and replaced by more specific designations.

### SUMMARY

An attempt has been made to picture the clinical aspects of hypertension. Some of the facts suggested to the examining physician by a blood pressure reading have been analyzed. Many of the conclusions have not been orthodox but tinged by personal interpretation. However, this is justified since the physiology and functional pathology of blood pressure are not entirely clear, and the formulation of workable theories in regard to blood pressure are necessary for the physician so that underlying conditions may be diagnosed and purposeful treatment may be carried out.

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## THE USE OF CONVALESCENT SCARLET FEVER AND MEASLES SERA IN PROPHYLAXIS AND THERAPY\*

WILLIAM THALHIMER

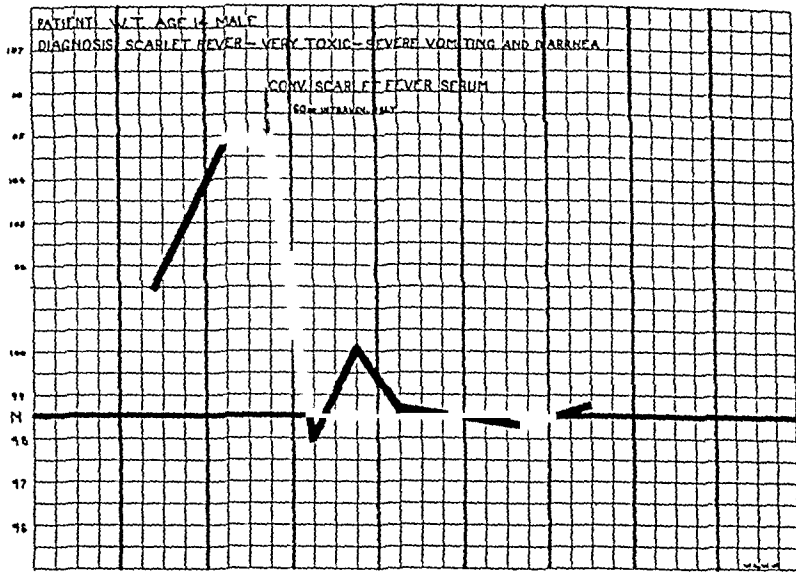
Manhattan Convalescent Serum Laboratory

IT is well known that an attack of certain infectious diseases confers lasting, even lifelong immunity on the recovered individual. These individuals, known as immunes, can have intimate contact with these infectious diseases and still not contract them. This resistance results because the disease has caused the active and continuous development of immune substances in the tissues or blood, or both, of the recovered individuals. These substances neutralize the infectious agent when it attempts to gain entrance into the body, and, thereby, prevent infection.

This natural method of the development of immunity has been utilized in some diseases for the preparation, in animals, of serums for preventing or treating specific, infectious diseases. Diphtheria antitoxin is an example of one of these serums prepared by inoculating horses with the diphtheria toxin, which stimulates the development of antitoxin, just as the clinical disease diphtheria causes this effect in patients who recover. Diphtheria antitoxin, when injected under the skin of a child exposed to this disease is almost 100 per cent efficient in preventing the development of diphtheria. In this way diphtheria antitoxin developed actively in the horse is transferred passively to the exposed child. The resulting passive immunity is a temporary one which lasts for two to three weeks. Although of a temporary nature it is extremely important immediately to protect susceptible children from diphtheria, especially young children in whom the mortality is high. Diphtheria antitoxin of course, also is very efficient therapeutically.

Weisbecker<sup>1</sup> in 1897 was the first one to find out that human serum obtained from an individual recently recovered from scarlet fever, when injected into another will cause a passive immunity, and also, will give excellent results with rapid cure in the treatment of patients in whom scarlet fever has already developed.

\* Delivered February 18, 1938 in the Friday Afternoon Lectures Series.



This serum has been named convalescent serum since it is prepared from the blood of individuals who are convalescing from or have recently recovered from infectious diseases. A better name is "convalescents' serum."

My interest in convalescent serums was aroused six or seven years ago for several reasons.

First. Several convalescent serums have been proved, by a large experience, in many places, to have marked efficacy in prophylaxis or therapy, or both.

Second. Convalescent serums, which, of course, are human serums, are safe agents to use and practically never cause reactions, even when administered intravenously. These properly prepared human serums have been demonstrated to be as nearly bland material for intravenous administration as anything known to me. Febrile reactions, chills or serum sickness are extremely unusual, occurring in not more than  $\frac{1}{2}$  to 1 per cent of the instances, and have never, to my knowledge, caused concern or alarm to the attending physician. Sensitization and anaphylaxis, in my experience, are unknown. All this is in contradistinction to the risks from the injection of animal serums, even though animal serums have been much improved in this regard in recent years. In our experience, there are no reactions at all following the intramuscular injection of the properly prepared human serums, with the possible exception of a very occasional, mild serum sickness from seven



to ten days later, which has never required medication

Third The field for investigation is extremely large, and needs intensive work

The serum is prepared according to the rigid regulations of the U S Public Health Service, and the laboratory, having satisfied these requirements, has received a federal license Only Wassermann negative serums, which have been proved bacteriologically sterile, are used These are pooled, usually in lots of thirty individual serums Preservative is added, followed by Berkefeld filtration and bottling Sterility tests are repeated on the bottled serum, and each pool is held at least seven days before being released by a negative sterility test

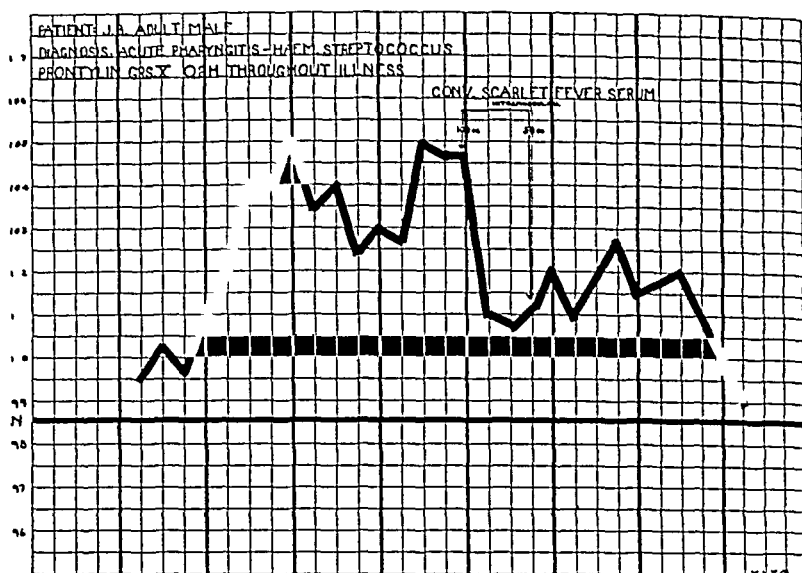
Extreme care and gentleness are used in handling the blood and serum, so as to prevent even a tinge of hemolysis, and bleedings are made only at least three hours after the donor's previous meal (so as to minimize the possibility of food proteins being present in the serum)

It is my conviction that these precautions have eliminated reactions from the use of these human serums practically to the vanishing point An experience of five years, covering thousands of injections of different types of convalescent serum administered by many physicians, both intravenously and intramuscularly, has demonstrated the practicability of preparing human serums which can be injected with no risk of severe reactions and with only the rare occurrence of a mild reaction

Since all blood cells are removed by Berkefeld filtration, there is no possibility of agglutinable cells being present and causing a reaction Also, whatever agglutinins the pooled serum contains, apparently are diluted sufficiently by the patient's entire circulating blood to prevent reactions This also is the explanation of why blood transfused from universal donors into type II or III recipients has not caused reactions (except possibly in rare instances)

The serum has not caused sensitization, even when injections have been given to children at ten day intervals to prevent the reappearance of measles in a children's institution With this procedure hospital wards can be kept open continuously even in the midst of epidemics

Only adult donors are used, except in times of great prevalence of these two exanthemata (scarlet fever and measles), when children of fifteen or over may be used, after receiving the signed consent of the parents Adults furnish 250 cc of blood (by vein puncture) at each bleeding for which they receive \$5 This yields a net of about 100 cc



of serum, after carrying out serological and sterility tests. The first bleeding can be made from recent convalescents after an afebrile period of seven days. Bleedings can be repeated in men at two week, and in women at three week intervals, without any deleterious effect and without any decrease in their hemoglobin percentage. Our data show that, on the contrary, the hemoglobin increases. It has been demonstrated that no significant fall in potency occurs in the serum secured from an individual for, at least, four months after onset in scarlet fever and measles. This period may be longer, and if investigation in progress demonstrates this, the source of supply will be correspondingly increased. Serum kept at four degrees centigrade retains its potency for at least a year.

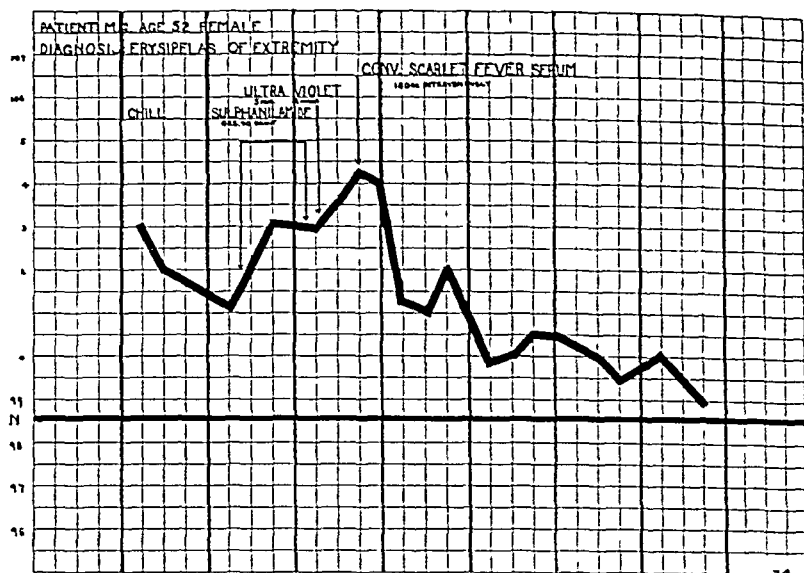
It might be well to discuss measles convalescent serum first.

Undoubtedly you will be interested to know that in 1916 Dr. William H. Park (with Zingher's cooperation) was the first in this country to employ convalescent serum for the prevention or attenuation of measles. This work was carried out independently, the same year as that of Nicolle and Conseil,<sup>2</sup> who published their results in 1918, Dr. Park not publishing until 1924.<sup>3,4,5</sup> Since these publications, more or less sporadic studies have been made in many places but only in recent years have centers been organized in a few European and American cities making enough convalescent serum available for extensive use. All of these trials, both small and large, have demonstrated the marked effi-

ciency of this method of measles prevention or attenuation

Measles is usually considered a mild disease, inconvenient but inevitable. Therefore, it might be surprising to learn that in infants up to one year of age, who contract measles, the mortality rate is 8 per cent, in the one to two year age group 5 per cent and in those from two to three years old 1.5 per cent. These fatalities are caused mainly by the not uncommon serious complications of measles, such as pneumonia and mastoiditis. But from ten years of age on the mortality rate is much less, yet not insignificant, i.e., 0.1 per cent to 0.2 per cent. Stated in another way, 95 per cent of all deaths from measles occur in children four years old and under. Accordingly, the older a child is when accidentally infected with measles, the less likely he is to suffer serious complications or death. One further illustration, quoted from Godfrey,<sup>6</sup> is very illuminating. In New York State, from 1915-1924 there were 35,930 cases of measles reported among children under three years of age, in places of less than 200,000 population. Of these, 1,441 died, a fatality rate of 4 per cent. Had these attacks of measles been postponed until the children were between five and fourteen years old, only fifty-four would have died and the lives of 1,387 children in this group would have been saved. In other words, if there were a method which did no more than allow one to postpone measles until after children reached their fifth year, many lives could be saved. Apparently, it is not generally known that such a method does exist. If used within five days after exposure, it can prevent the disease in up to 95 per cent of those exposed, thereby postponing the contraction of measles till the children are older and in a more resistant age group when again accidentally exposed. The method has the further advantage, that if used within one week after exposure it can modify the infection to a mild, attenuated measles, practically sure to be free from serious complications. This attenuated measles is often so mild that it is difficult to diagnose, and yet the attenuated attack apparently confers sufficient permanent active immunity to prevent the disease occurring again.

It has been shown that the maximum percentage of prevention is achieved only if the serum is injected intramuscularly within five days after exposure. The minimum dose for children five years old or less is 5 cubic centimeters and for older children one cubic centimeter for every year of their age. Prevention can then be expected in from 70 per cent to 95 per cent of the injected children. Even in those instances



where complete prevention does not occur, a modified and attenuated attack will occur in all but 3 per cent to 5 per cent of the total group. One can readily see the advantage of limiting measles in healthy children to this mild disease with its subsequent immunity. As a matter of fact, attenuation should be the method of choice except in debilitated or sick children, in children five years of age or less, and in children exposed accidentally in hospitals and institutions. The reason for attempting complete protection in all children not over five years old, even though they are robust and in good health, is that the mortality from measles is confined mainly to this lower age group.

The full dose of serum has some chance of preventing the disease even if administered between the fifth and seventh day after exposure, and even if it fails to prevent the disease, usually causes attenuation. On and after the eighth day of exposure very little protection can be expected.

For attenuation, which is advised as the method of choice in healthy children over five years of age, one-half of the usual dose of serum should be injected not later than the fifth day of exposure, or the full dose from the sixth to the seventh day.

It also is well known that pooled normal adult serum is as efficient in the prophylaxis of measles as the specific convalescent serum, but it must be used in four times the amount, and normal whole blood in about eight times the quantity.<sup>7,8</sup> The disadvantage, formerly, in using normal

serum was the larger amount which had to be injected

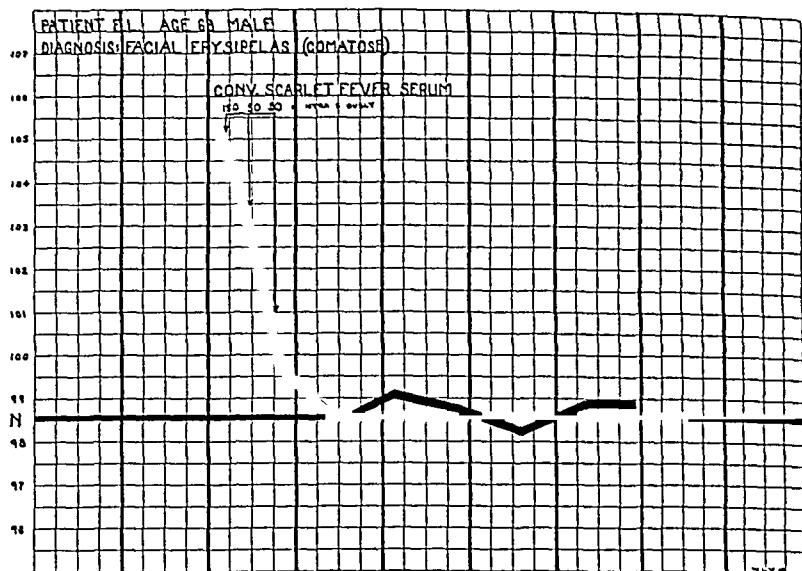
However, now we have several methods available for concentrating serum, and, thereby, reducing the amount of immune measles serum to be injected to the same volume needed when convalescent serum itself is injected. One method, which was developed recently in our laboratory, is by concentrating the serum in sterile, viscose casings, another is by precipitating the globulin of the serum, which was investigated by Dr Samuel Karelitz<sup>9 10 11</sup> with the cooperation of Dr K G Falk and Mr C Greenwald of the Research Laboratory of the Department of Health in the preparation of the globulin fraction. There, also, are several methods of freezing and drying serum, and redissolving it in a small amount of sterile distilled water.

There is no other method of preventing measles except with material obtained from human blood or similar sources (placental globulin,<sup>12 13</sup> with which I have had no experience).

In 1914, again it was Dr Park who carried out the first work in this country with convalescent scarlet fever serum. This work was done under his direction by Zingher.<sup>14 15</sup>

Many reports since, in many countries, have shown the marked therapeutic value of pooled convalescent scarlet fever serum when this is given in large enough amounts and especially when administered intravenously early in the disease. The beneficial results have been so definite that in many articles recommendations are made for the organization of agencies for collecting and distributing convalescent serum. Blood, yielding potent serum, can be drawn on the twentieth day after the onset of illness, provided the patient is convalescing and has been fever free for at least seven days, and further bleedings may be made at two or three week intervals for a period of four months from the onset of the illness. About eight years ago, with the cooperation of the Chicago Department of Health and of a number of colleagues, and with a grant of funds, it was possible for me to organize the Samuel Deutsch Convalescent Serum Center at Michael Reese Hospital, and similarly, three years ago the Milwaukee Convalescent Serum Center at Columbia Hospital, Milwaukee. Some of the observations in Chicago have been published with Hoyne and Levinson.<sup>16</sup>

Eight hundred and seventy-two children, giving no previous history of scarlet fever, and unavoidably exposed in their homes to this disease, were passively immunized with from 10 to 20 cc of pooled convalescent



serum, and only 2 per cent developed mild scarlet fever and 1 per cent genuine scarlet fever. In similarly exposed home contacts, Park states that in his experience about 10 per cent contract scarlet fever, and Gordon's findings in Detroit were 15 per cent. From 90 to 93 per cent were protected who were expected to contract the disease.

The doses for prophylaxis which we are recommending and which seem to be giving excellent results are 10 cc by intramuscular injection to children up to five years of age, 15 cc to those whose age is from five to ten years and 20 cc for older children.

The results of therapy have been published of 947 severely ill hospitalized patients and 983 home treated patients of varying degrees of severity, 1,930 patients in all. The hospitalized patients were treated in the Chicago Municipal Contagious Disease Hospital under the direction of Dr. Hoyne.<sup>10</sup> Only severely sick patients received serum, usually on admission, and 6,282 mildly or moderately ill patients, admitted to the hospital during the same period, treated symptomatically and not receiving serum, served as controls.

Some of the findings can be briefly re-stated. Patients without septic complications showed an average fall of temperature of two and a half degrees in the first twenty-four hours and a total of three degrees in the first forty-eight hours when they received the convalescent serum within the first three days of their illness.

Not infrequently the disease was rapidly aborted, and even a toxic

patient with a temperature of 104-105 degrees was converted in twelve hours into a convalescent patient, with normal temperature, followed by an uninterrupted rapid convalescence

When the serum was given from the fourth to sixth days of the disease the temperature drop was from one-half to one degree less. With the decline of temperature in the patients treated early, there was a corresponding and marked diminution of toxicity, fading or disappearance of the rash, relief from angina, nausea and vomiting, return of appetite, and shortening of the period of illness. Most patients with complications on admission or mildly ill but later developing complications were also greatly benefited by serum.

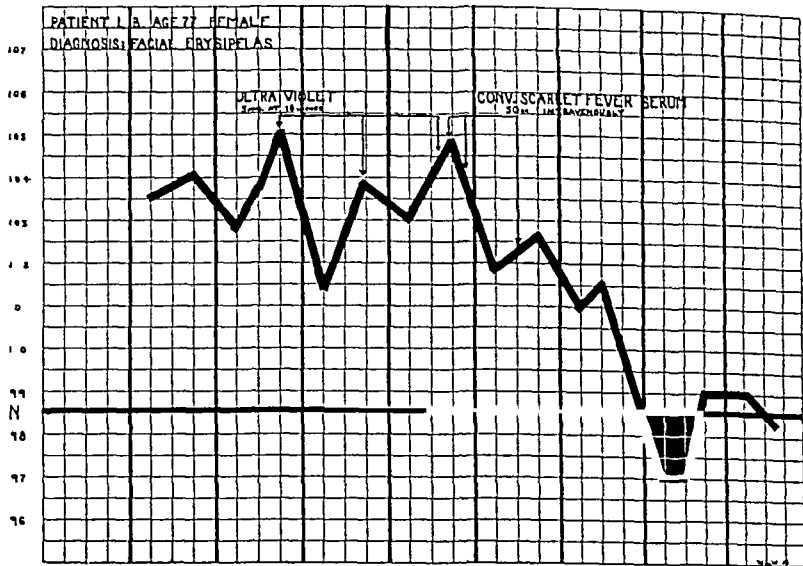
The evidence definitely shows also that severely ill, serum treated individuals developed a smaller number of less severe complications than the mildly or moderately ill in the control group not receiving serum.

The dosage, depending on the size of the individual and the severity of the illness, varied from 20 to 100 cc. It was administered intravenously and occasionally had to be repeated.

The value of intravenous administration over the intramuscular method cannot be over-emphasized. When the serum is injected into the vein it is distributed immediately throughout the entire blood stream and entire body. Hence, therapeutic action begins immediately. However, it takes from fourteen to sixteen hours for maximum absorption to occur after intramuscular administration, and even then the potency of the serum in the blood is only one-half of what it would have been had the same dose been given into the vein. It is the safety with which one can administer human serum that allows us to recommend the intravenous method rather than any other.

It is well recognized that a specific, therapeutic serum must be administered early in the course of an infectious disease, in order to secure maximum curative results. This holds just as true with the early administration of convalescent scarlet fever serum as with any other serum, such as diphtheria antitoxin. If one is to use convalescent scarlet fever serum therapeutically in severely ill scarlet fever patients, this serum should be administered in proper doses intravenously as soon as the diagnosis is made.

Another important use of convalescent scarlet fever serum is in the treatment of various types of hemolytic streptococcal infections.



other than those arising from scarlet fever<sup>17</sup> The reason for this, apparently, is that virulent, hemolytic streptococci causing various types of infection are closely related to those occurring in scarlet fever They give rise to similar toxins which are neutralized by similar antitoxins

Since the convalescent serum laboratory has been opened in New York, many physicians have used convalescent scarlet fever serum, on our advice, in the treatment of a large number of patients with severe streptococcal infections of the limbs, with streptococcal pneumonia, with severe forms of erysipelas, with streptococcal blood stream infections, and other serious types of streptococcal infections All of these patients have been desperately ill, and the lives of many have been despaired of, even after all other types of treatment have been used Many of these patients have made rapid recovery Considering the desperate plight of these patients the physicians have considered many of these results to be quite startling A statistical analysis of these results is impossible, because it is impossible to secure a control group of similar patients Once a therapeutic agent is known to be of value it cannot be denied to anyone, and, therefore, the observation of a control, untreated group is impossible One can estimate the significance of the results on the basis of previous experience

Recently a very remarkable drug, sulphanilamide, has been extensively used in the treatment not only of streptococcal infections, for which it was introduced originally, but for other types of infection as



well Many of the results with sulphanilamide treatment have been remarkable, but peculiarly enough it has been found by a number of observers to cause very little or no benefit in the treatment of scarlet fever<sup>18</sup> It has been found, also, that sulphanilamide, at times, causes toxic effects and may even cause disaster, therefore, this potent drug must be used with care and at times must be discontinued Some of the results referred to above in the treatment of patients desperately ill with various types of streptococcal infections have been achieved when sulphanilamide failed or when sulphanilamide had to be discontinued

It should be emphasized again that convalescent serum is as nearly bland and innocuous a material as we know of, and, when properly prepared, in our experience has never produced any bad effects, which caused concern to the attending physicians Whereas the exact method of action of sulphanilamide is not known, some experimental work by Rosenthal<sup>19 20</sup> indicates that a specific, therapeutic serum may complement the action of sulphanilamide, so that these two substances act synergistically This means that when given together the beneficial effect is greater than the summation of the effect of each given separately Therefore, during the past year since sulphanilamide has been available, some patients have received both of these agents simultaneously with excellent results

It has been found that convalescent scarlet fever serum is an excellent material for producing the Schultz-Charlton blanching phenomenon, which, at times, is an important aid in the diagnosis of a scarlet fever rash One cubic centimeter of this serum should be injected intracutaneously, and this small amount of serum, put up in ampoules, can be obtained at our laboratory Again the use of human serum for this test avoids the use of animal serum with the possibility of reactions, sensitization, etc

The Manhattan Convalescent Serum Laboratory is located in the Research Laboratory of the City Department of Health, on the same grounds where Dr Park years ago did the first work in this field in this country It is a non-profit organization, and its work has been made possible by the grant of funds from the Nathan Hofheimer, New York and Friedsam Foundations, and the Lederle Laboratories

In order to maintain a supply of serum it is necessary to charge the cost of production of these serums Until now the laboratory has not become self-supporting, but it is hoped that it will become so in the

future

The demand for serum by physicians and hospitals has become so great that it is only with the greatest difficulty that we have been able to secure a sufficient supply to satisfy these demands. We need the help of all physicians in our endeavors to secure a sufficient amount of convalescent serum. Physicians can be of the greatest service in advising their private adult and adolescent patients immediately after recovery from measles or scarlet fever to cooperate with the Manhattan Convalescent Serum Laboratory. Only 250 cc of blood are taken at a time, and for this each donor is paid \$5 immediately. In our experience with many thousands of donors this has never caused the donor any harm. Since we take special care to make this a painless procedure with a small intracutaneous injection of novocain, the donors willingly return at three-week intervals for a period of four months to do their share in furnishing serum to aid others, especially children, exposed to or suffering from the disease from which the donors have just recovered. Physicians, also, have been extremely cooperative in advising their patients to help in this work.

The laboratory appreciates the help that has been given by many physicians, and will endeavor to maintain its effort to cooperate with physicians and hospitals in the control and treatment of infectious diseases.

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## PROCEEDINGS OF ACADEMY MEETINGS

## STATED MEETINGS

MAY 5—*The New York Academy of Medicine* Executive Session—a] Reading of the minutes, b] Presentation of diplomas ¶ Joint meeting of The New York Academy of Medicine and the Welfare Council of New York City, Presiding James Alexander Miller, president, The New York Academy of Medicine—c] Chronic illness in New York City Findings of the National Health Survey, G St J Perrott, principal statistician, National Health Survey of the United States Public Health Service, b] A community program for the care of the chronically ill Based upon the hospital survey for New York, Ernst P Boas, chairman, Committee on Chronic Illness of the Welfare Council of New York City ¶ Report on election of members

MAY 19—*The Harvey Society* (in affiliation with *The New York Academy of Medicine*) The eighth Harvey Lecture, Experimental Hypertension Induced by Renal Ischemia, Harry Goldblatt, Professor of Experimental Pathology, Western Reserve University

## SECTION MEETINGS

MAY 3—*Dermatology and Syphilology* Executive Session—a] Reading of the minutes, b] Election of section officers and member of Advisory Committee—For chairman, Eugene F Traub, for secretary, Louis Fulpan, for member of Advisory Committee, Max Scheer ¶ Presentation of cases—a] New York Polyclinic Hospital, b] Beth Israel Hospital, c] Good Samaritan Dispensary, d] Sea View Hospital, e] Miscellaneous cases ¶ Discussion of selected cases

MAY 6—*Surgery* Executive Session—a] Reading of the minutes, b] Election of

section officers and member of Advisory Committee—For chairman, Frank L Meleney, for secretary, J William Hinton, for member of Advisory Committee, Roderick V Grace ¶ Presentation of cases ¶ Papers of the evening—a] After treatment of Colles' fracture, Frederick Henry Amendola, Discussion by Condict W Cutler, b] Problems in treatment of fractures in children, Fenwick Beekman, John E Sullivan, c] Preliminary report on a new pin method for treatment of fractures of shafts of the long bones, Kenneth M Lewis, Lester Breidenbach, d] Open reduction and fixation as a primary procedure in adult fractures of the long bones, Clay Ray Murray, Discussion by William Darrach ¶ General discussion

MAY 10—*Joint Meeting, Neurology and Psychiatry and the New York Neurological Society* Executive Session, Section of Neurology and Psychiatry—a] Reading of the minutes, b] Election of section officers and members of Advisory Committee—For chairman, Morris Grossman, for secretary, Lewis Stevenson, for two members of Advisory Committee, George H Hyslop, for two years to fill unexpired term of James H Huddleson, resigned, Irving H Pardee, for five years ¶ Papers of the evening—a] On the topography of a probable sleep-regulating center, Joseph H Globus, Discussion by Henry A Riley b] The treatment of neurogenic megacolon by selective drugs, Walter O Klingman Discussion by Edward J Donovan, Angus M Frantz, Henry A Riley c] Psychopathological aspects of emotional divorce, Philip R Lehrman Discussion by Clarence P Oberndorf, Louis Casamajor, Irving Pardee, Israel Wechsler, S Bernard Wortis, George Hyslop, Simon Rothenberg (by invitation) ¶ General discussion

MAY 11—*Historical and Cultural Medicine*  
Executive Session—*a*] Reading of the minutes, *b*] Election of section officers and member of the Advisory Committee—For chairman, Howard Reid Crug, for secretary, Louis Casamajor, for member of the Advisory Committee, Reginald Burbank ¶ Papers of the evening—*a*] Medieval origins of the modern hospital (Intern slides), Edward F Hartung, *b*] Konrad Gesner—scholar physician (Intern slides), Thomas P Fleming (by invitation) ¶ General discussion

MAY 12—*Pediatrics* Case Demonstrations  
¶ Executive Session—Election of section officers and member of Advisory Committee—For chairman, Philip M Stimson, for secretary, Lucy Porter Sutton, for member of Advisory Committee, Samuel Z Levine ¶ Presentation of single case reports—*a*] Israel Zion Hospital—Esophageal varices and thrombosis of the splenic vein, H M Greenwald, *b*] New Rochelle Hospital—Hemorrhagic disease of the new born, Fairfax Hall, *c*] Babies' Hospital—Dermatomyositis, Ralph V Platou (by invitation), *d*] Mount Sinai Hospital—Lipoid granulomatosis, Howard G Rapaport (by invitation), *e*] New York Infirmary for Women and Children—Unusual carbohydrate metabolism, Marion Joseph (by invitation), *f*] New York Hospital—Dermatorrhexis (Ehlers-Danlos syndrome), Carl H Smith, *g*] Roosevelt Hospital—Post-infectious cervical subluxation, Alexander T Martin, M Beckett Howorth, *h*] Willard Parker Hospital—Mastoiditis in scarlet fever with ligation of the common carotid artery, Francis W White, *i*] St Luke's Hospital—Injury of child by roentgen rays during pregnancy, F Elmer Johnson, *j*] Post-Graduate Hospital—A variety of spotted fever, Irving Posner (by invitation), *k*] Metropolitan Hospital—Tuberculous meningitis resembling diabetic coma, Louis L Krafchik (by invitation), *l*] Lenox Hill Hospital—Gangrenous cholecystitis with perforation,

Irwin P Sobel, Discussion by J Leopold, *m*] Knickerbocker Hospital—Intussusception with presentation of appendix at anus, Irving LeBell (by invitation), *n*] Harlem Hospital—Congenital obliteration of the bile duct, Reuben Steinholz (by invitation), *o*] Flower-Fifth Avenue Hospital—Osteopetrosis (Albers-Schönberg's disease), Morris L Chick (by invitation), Discussion by M Biss, *p*] Bronx Hospital—Icterus gravis, Henry M Weissmann (by invitation), I Rothstein (by invitation)

MAY 16—*Ophthalmology* Examination of cases (bring instruments) ¶ Executive Session—*a*] Reading of the minutes (8 15), *b*] Election of section officers and member of Advisory Committee—For chairman, James W White, for secretary, Rudolf Aebli, for member of Advisory Committee, Martin Cohen ¶ Paper of the evening—The intraocular tension in sarcoma of the choroid and ciliary body, John H Dunnington ¶ Case reports—*a*] Trauma with secondary orbital infection and retinal changes, *b*] Lymphoma or Mikulicz's disease of the lacrimal glands, *c*] Hypertelorism (this case shows wide-spread orbits and distinctive x-ray findings), Webb W Weeks, *d*] Anomalous retinal vein crossing the macula, A L Kornzweig (by invitation), *e*] Precancerous melanosis of the lids and conjunctiva, Algernon B Reese, *f*] Disappearance of the iris after prolonged hyphemia, *g*] Fistula of the lacrimal gland, Guernsey Frev, *h*] Sudden dislocation of the lens in the anterior chamber, of congenital origin in two members of a family, followed by secondary glaucoma, Extraction of lenses, *i*] Unilateral exophthalmos due to a sclerosing sarcoma of the interior middle cranial fossa, Martin Cohen, *j*] Tra-Sachs disease, Joseph Lival, *k*] Zonular opacity of the cornea, M Davidson, *l*] Retrobulbar neuritis with partial closure of the central retinal artery, Walter F Duggan (by invitation), *m*] Retinitis punctata albescens, *n*] Keratitis neuroparalytica, Morris Jaffe (by



invitation), o] Diarrhoedenitis, Henry Minsky, p] Superficial punctate keratitis in a young boy, q] An interesting fundus lesion, r] Ankyloblepharon with heterochromia of the iris, R Townley Paton, McClelland Shellen (by invitation), s] Occupational kerato-conjunctivitis in a brass worker, Frances Richman (by invitation) t] Von Hippel's disease (angiomas of the retina), Benjamin C Rosenthal (by invitation), u] Retinitis pigmentosa Hole in macula of one eye, v] Bilateral glaucoma controlled by a LaGrange iridectomy, Charles A Perera (by invitation) w] Photographic studies of a case of intraocular foreign body before and after removal, Donald W Bogart (by invitation), x] An operation for congenital ptosis, Giacomo Bonaccolto, y] Proptosis in a six weeks old infant, Morris Greenberg

**MAY 17—Medicine Executive Session**—Election of section officers and member of Advisory Committee—For chairman, Thomas T Mackie, for secretary, Samuel W Lambert, Jr, for member of Advisory Committee, Joseph Hisek ¶ Papers of the evening—a] The diagnosis and treatment of gonorrheal endocarditis, John S Davis, Jr, Discussion by Ralph H Boots, b] Oil aspiration pneumonia and pneumolipoidosis, Philip G C Bishop, Discussion by H Pinkerton, Boston (by invitation), c] The therapeutic aspects of gastric and duodenal ulcer with hemorrhage, Burrill B Crohn, Henry H Lerner (by invitation), Discussion by William H Glafke

**Genito-Urinary Surgery** No meeting of the section of Genito-Urinary Surgery was held in May ¶ The following section officers and member of the Advisory Committee were elected at the meeting of the section held April 20 Chairman, John A Taylor, secretary, Simon A Beisler, member of Advisory Committee, Roy B Henline

**MAY 18—Otolaryngology Executive session**—a] Reading of the minutes, b] Elec-

tion of section officers and member of Advisory Committee—For chairman, Francis W White, for secretary, Fred W Graef, for member of Advisory Committee, John D Kernan ¶ Paper of the evening—Affections of the cricopharyngeal fold, Mr Victor E Negus, London, England (by invitation), Discussion by John D Kernan, Charles J Imperatori ¶ General discussion

**MAY 20—Orthopedic Surgery Executive session**—a] Reading of the minutes, b] Election of section officers and member of Advisory Committee—For chairman, Joseph B L'Episcopo, for secretary, David M Bosworth, for member of the Advisory Committee, Earl E VanDerwerker ¶ Papers of the evening—i] Athletic injuries, Marvin A Stevens (by invitation), b] Analysis of three hundred and thirty cases of supracondylar fractures from the Children's Surgical Service of Bellevue Hospital, Irwin E Siris, c] Hoke arthrodesis for flaccid flat feet in children, Peter E Sabatelle (by invitation) d] Demonstration of motor bone unit, S Lloyd Fisher (by invitation) ¶ Discussion

**MAY 24—Obstetrics and Gynecology Executive session**—a] Reading of the minutes, b] Election of section officers and member of Advisory Committee—For chairman, Edward H Dennen, for secretary, Alfred M Hellman, for member of Advisory Committee, Louis J Ladin ¶ Papers of the evening—a] Autopsy findings in still-births and neonatal deaths a report of 200 cases, John W Hammond Discussion by Anthony Rotunno (by invitation) b] A critical analysis of blood loss following delivery, with special reference to the value of ergotrite, Arthur M Reich Discussion by Harvey B Matthews, John B Pastore (by invitation), c] Further observations on the endocrine basis of toxemia of pregnancy, with a classification of hypertension in pregnancy, Jefferson J Vorzimer (by invitation), Discussion by William Herrick, Raphael Kurzkroh

## AFFILIATED SOCIETIES

MAY 16—*The New York Roentgen Society* (in affiliation with *The New York Academy of Medicine*) Interesting cases ¶ Paper of the evening—X-ray diagnosis of functional foot disorders, Dudley J Morton (by invitation), Discussion opened by T Campbell Thompson (by invitation) Maurice M Pomerantz ¶ Executive session—Annual meeting and election of officers

MAY 18—*New York Section of the Society for Experimental Biology and Medicine* Variations in pathways by which equine encephalomyelitis viruses invade the CNS of mice and guinea-pigs, Albert B Sabin, Peter K Olitsky ¶ Age of host and capacity of equine encephalomyelitis viruses to invade the CNS, Albert B Sabin, Peter K Olitsky ¶ Effect of age of the host on resistance to tuberculous infection, K C Smithburn ¶ Effects on blood pressure of injections of urine extracts of normal and hypertensive individuals, J H Leatham (Introduced by W W Swingle) ¶ The un-

identified base in gelatin, Donald D Slyke, Alma Hiller (by invitation), Robert T Dillon (by invitation), Do MacFavden (by invitation) ¶ Transmission of mouse sarcoma with numbers of counted cells, Morton Kahn, Jacob Furth ¶ "Acid" phosphate activity of the serum of normal man subjects, Alexander B Gutman, Ethel Benedict Gutman (by invitation) ¶ Business session

MAY 26—*New York Pathological Society* (in affiliation with *The New York Academy of Medicine*) Papers of the evening—a) Classification of the pathology of infected abortions, Henry C Falk (by invitation), b) Experimental studies of tissue reactions to lipids the formation of acid-fast membranes around certain oils and waxes, Irving Graef, William Kaufmann (by invitation), Leo Kaplan (by invitation), c) Disseminated lupus erythematosus in a male with some unusual findings, Arthur Ginzler (by invitation), T T Fox (by invitation) ¶ Executive session

## MEMBERS ELECTED

APRIL 8, 1938

## MEMBERS

Max Bernanke, 239 Central Park West  
Louis Berk, 215 East 73 Street  
Edwin B Bilchick, 876 Park Avenue  
John G Copeland, 24 Dove St, Albany  
Caldwell B Esselstyn, 16 East 90 Street  
Donald Malven  
7 Adriance Ave, Poughkeepsie

Frank Ober, 234 Marlborough St, Boston  
Gerald H Pratt, 219 West 44 Street  
Jeremiah T Simonson  
365 West End Avenue  
Thomas J White, 221 Union St, Jersey City

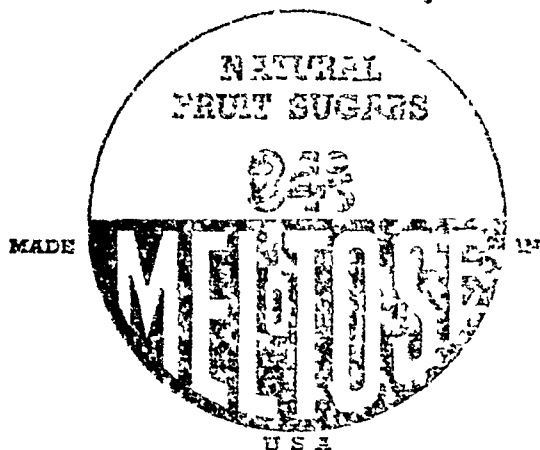
MAY 5, 1938

William Travis Gibb, Jr, 140 East 54 Street  
William H Resnik  
65 South St, Stamford, Conn  
Samuel B Schenck, 876 Park Avenue

## ASSOCIATES

Franklin Hollander, 203 West 81 Street  
William C MacFavish  
142 Edgemont Rd, Scarsdale, N Y

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